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ORIGINAL ARTICLES.

THE MEDICAL AND SOCIAL APPROACHES TO THE PROBLEM OF CHRONIC RHEUMATISM.*

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History. Chronic rheumatism is perhaps the oldest of all known diseases. In the Museum of the University of Kansas is the skeleton of a large swimming reptile, the mosasaurus, whose foot is said to show the lesions of chronic rheumatism. The beast is supposed to have lived 600,000,000 years ago. The Ape Man of the Pliocene period, a mere 2,000,000 years old, the Java and the Lansing men, our own ancestors of only 500,000 years ago, had chronic rheumatism of the spine and so did the Predynastic Nubians[24,33,37] and ancient Egyptian mummies of 8000 years before Christ, and the pre-Columbian Indians of America. We are back in the United States.

The name of these protean diseases, chronic rheumatism, is derived from the Greek word ῥεῦμα, meaning humor. The shade of Galen still stalks; it challenges us to find the solutions of the problems which these diseases still present, but as we tackle them we may perhaps take heart by remembering the aphorism of William the Silent, "It is not necessary to have hope to begin nor success to persevere."

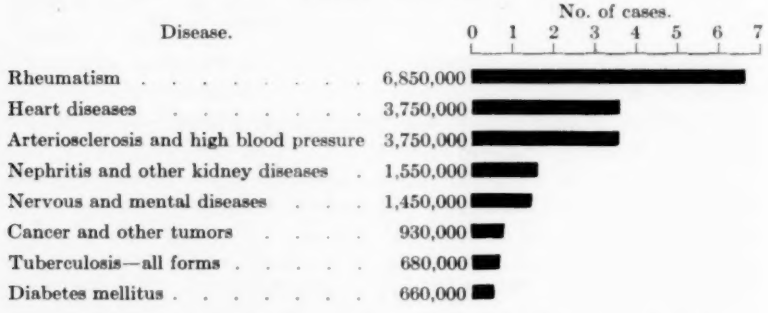
Incidence. Chronic rheumatism seems to be much more prevalent in the Temperate Zones than in the regions near the Poles or the Equator. Its incidence is greater in chill, damp climates than in high and dry regions, but it is a wellnigh universal disease.

The State Department of Public Health in 1930 made a survey of the incidence of chronic disease in Massachusetts the population of which is about 4,250,000. It was estimated that 6500 years of work and nearly $8,000,000 worth of wages are lost every year

* The Nathan Lewis Hatfield Lecture of the College of Physicians of Philadelphia, delivered May 1, 1940.

in this small state because of the ravages of chronic rheumatism. Rheumatism was the greatest single cause of chronic disease in Massachusetts.[4a] The National Health Survey of 1935 and 1936[25] seems to prove that of the chronic diseases "rheumatism," including in that term, arthritis, gout, "neuritis," "neuralgia," "lumbago" and probably "fibrositis," stands first in prevalence, first as the cause of disability (if mental cases be excluded), second as to permanent invalidity, but only fourteenth as a cause of death. As Bigelow and Lombard say,[4b] "Rheumatism then cripples in the largest number of cases and kills in the smallest. This very ability to cripple without killing would seem to put it in the lead of all other chronic diseases as of preëminent social, economic and medical importance." The social implications of this statement are evident. The editors of the Fifth Rheumatic Review well say, "Thus by all accounts 'rheumatism' is still the chief contender for the title of 'King of Human Misery.'"[20]

CHART 1.—ESTIMATED PREVALENCE OF SPECIFIED CHRONIC DISEASES IN THE UNITED STATES (1937).


Disease.
No. of cases.
0 1 2 3 4 5 6 7
Rheumatism 6,850,000
Heart diseases 3,750,000
Arteriosclerosis and high blood pressure 3,750,000
Nephritis and other kidney diseases 1,550,000
Nervous and mental diseases 1,450,000
Cancer and other tumors 930,000
Tuberculosis—all forms 680,000
Diabetes mellitus 660,000

The relative importance of chronic rheumatism may be appreciated when we compare its prevalence with the incidence of several of the other common chronic diseases. The incidence of heart disease proper is only about one-half that of chronic rheumatism. The same may be said of arteriosclerosis. There seem to be more cases of chronic rheumatism in the United States today than the sum total of all those persons affected by cancer, diabetes and all forms of tuberculosis early and late.

Medicine's Attack on the Problems of Chronic Rheumatism. Physicians must have recognized ῥεῦμα before medical history began, for we know that Hippocrates made an attempt to differentiate what Radulphe later called "gout" from chronic rheumatism. Men dreaded its inroads before the Christian era. With Gaius Catullus they prayed, "Save me, oh, save me, from this vile disease."

Sydenham in 1683 differentiated chronic rheumatism not only from gout but also from rheumatic fever. Heberden (1782), Haygarth (1802), Charcot (1853), Robert Adams (1857), the two

Garrods, A. B., the father (1859) and Sir Archibald E., the son (1890), Bannatyne (1896), Pribram (1902), Goldthwait (1904),[17] Hoffa and Wollenberg (1908), all studied carefully the clinical pictures of these diseases and added to our biochemical and pathologic knowledge of it. In 1906, however, T. S. P. Strangeways,[38] Lecturer on Special Pathology in the University of Cambridge, England, was able to open the first Research Hospital for the study of chronic rheumatism. Six years later he had accumulated notes on 4000 cases of rheumatoid arthritis and assembled in a small museum 2000 specimens of arthritic joints.

The greatest increment of knowledge was furnished by the beautifully illustrated monograph of Nichols and Richardson on "Arthritis Deformans," published in 1909.[26] This gave us the first clear and convincing picture of the essential morbid tissue changes associated with what we now call atrophic or rheumatoid arthritis and hypertrophic arthritis or degenerative joint disease. The work of these investigators has never been gainsaid. The more recent work of Allison and Ghormley[2] and other pathologic research, based on a greater material and carried out with more modern methods of tissue study, have given us more details and confirm the original work of Nichols and Richardson.

The active interest of internists and practitioners grew very slowly. The arousing and maintenance of the interest of medical men is, to a very large extent, due to the work of one of your Fellows, Dr. Ralph Pemberton.[28] I believe that to him more than to any other man we owe the sustained renaissance which has occurred in the study of chronic rheumatism.

The renaissance continues abroad and at home. Before the onset of the European War there were 27 branches of the International League for the study of rheumatic diseases in Europe and in the continents of North and South America. The Sixth Congress of the Ligue Internationale was held in London and Oxford and Bath in 1938. Plans were well under way to hold the Seventh Congress, under the presidency of Dr. Pemberton, in Philadelphia, New York and Boston in June, 1940. In times of peace we shall look forward with pleasurable anticipation to the completion of our plans.

The Lovett Foundation in Boston helped materially by grants from the Department of Public Health of Massachusetts and by the Commonwealth Fund, the Rackham Arthritis Research Unit of the University of Michigan, and many special arthritic or rheumatic clinics all over the country for the study and treatment of these diseases, are constantly adding to our knowledge and bringing surcease to their patients. There are at present two journals devoted to rheumatism in England. The British Rheumatism Committee also frequently issues bound volumes reporting significant clinical and laboratory research. Six American reviews of English and American medical literature dealing with the rheumatic diseases

have been published and are models of thoroughness and in the value of their editorial comment. We have found "hope to begin" and perhaps may be said to have had a little success in persevering.

Classification of Chronic Rheumatic Diseases. I fancy we should all agree that the most helpful classification would be one based upon etiology. Our present lack of knowledge as to specific causes of these diseases forbids such a classification. For the moment we may be content with a "working" classification and perhaps the one suggested by this chart may be as useful as any. Most of our serious medical and social problems are to be met in dealing with the two (possibly three) most common types in which the exact etiology may be said to be unknown.

CHART 2.—WORKING CLASSIFICATION OF ARTHRITIS.

I. Origin known:
   1. Traumatic, *e. g.*, due to internal derangements of joints, fractures into joints, etc.
   2. Infectious, *e. g.*, due to tubercle bacillus, gonococcus, streptococcus, staphylococcus, etc.
   3. Neuropathic, *e. g.*, due to tabes, syringomyelia, leprosy, etc.
   4. Arthritis associated with metabolic or constitutional diseases, *e. g.*, hemophilia, gout, etc.
   5. Anaphylactic or allergic, *e. g.*, associated with serum sickness.
   6. "Fibrositis," "fascitis," tenosynovitis, etc., of known origin.

II. Origin not certainly known:
   1. Rheumatoid, proliferative or atrophic arthritis.
   2. Hypertrophic, degenerative or osteoarthritis.
   3. Rheumatic fever.
   4. "Fibrositis," "fascitis," tenosynovitis, etc., of unknown origin.

To an increasing majority of trained and open-minded observers, it seems almost certain that chronic rheumatism of the atrophic or rheumatoid type and chronic rheumatism of the hypertrophic or degenerative joint disease type are distinct and separate diseases. Virchow apparently believed them to be different manifestations of a single syndrome and grouped them under the name of "arthritis deformans." As they both do deform the joints, the casual medical observer remains satisfied with the name. We shall do well not to close our minds to the possibility that many similar etiologic factors may influence the onset of both diseases. For the betterment of both, many similar therapeutic methods are applicable.

We are of the opinion that there are many reasons for believing that "Still's disease" or "Felty's syndrome" associated with lymphoid hyperplasia, represents only a rather rare manifestation of atrophic or rheumatoid arthritis occurring in children. Many careful observers have reached the conclusion that the condition variously designated as spondylitis deformans, Marie-Strümpell syndrome, *spondylose rhizomelique* or *spondylose ankylopoietica* is also only a somewhat unusual form of atrophic or rheumatoid arthritis the chief manifestations of which are commonly confined to the spine. Your speaker inclines to the belief that spondylitis deformans may yet be found to represent a third distinct syndrome of

chronic rheumatism. We will not labor the point but simply call attention to its peculiar lesions, especially of the almost constant ossification of the anterior common ligament of the spine and to the fact that whereas atrophic or rheumatoid arthritis affects women much more often than men, spondylitis deformans attacks men much more often than women in a ratio variously estimated from 1 in 5 to 1 in 10.

Etiologic Concepts. We shall attempt to discuss the etiologic concepts which have influenced the treatment of these diseases in the past and those which obtain at present.

Diathesis. The hand of the Lord was first believed to be the chief cause of chronic rheumatism. Alas, many physicians still have a strong tendency to incriminate the Lord. The ῥεῦμα or humoral theory of Galen is dead, but the almost equally vague theory of a rheumatic diathesis persists and cannot yet be completely denied.

Infection. Since Pasteur's discovery of microbes the infectious theory has been widely accepted, strengthened chiefly by the articles of Billings[5] and Miller in 1916, of Burbank and Hadjopoulos in 1925,[6] of Cecil, Nicholls and Stainsby in 1929,[8a] and of Small in 1930.[36] It has been held that even in the absence of frank "rubor, calor and dolor," the essential etiology of acute and even chronic rheumatism could be explained by the existence of not only evident but also hidden foci of infection. The most common habitats of these foci were thought to be the teeth, the tonsils, the sinuses, the gall bladder, the genito-urinary and the alimentary systems. The theory of focal infection is not a new theory, for we find the physician of Ashur-bani-apal, King of Assyria, in the seventh century before Christ, giving his master the following advice: "He will speak the truth with the king as the king demanded: the pain in his head, his sides and his feet has come from his teeth, they must be extracted." The brilliant work of Cecil and his colleagues,[8b,27] in connection with the positive agglutination reactions to hemolytic streptococcus obtained from a very high percentage of the sera of atrophic or rheumatoid cases, convinced them that some form of streptococcus was the usual causal agent. However, Dawson, Olmstead and Boots,[12] after confirming Cecil's agglutination reactions and admitting their strong etiologic suggestiveness, were unable to evaluate the *significance* of these findings. Tillett, Abernethy and Fisher[39] had called attention earlier in this same year to the fact that sera derived from patients acutely ill with various bacterial infections are capable of reaction to certain strains of hemolytic streptococci. Several investigators have reported high percentages of positive findings of streptococci in the blood and joints of atrophic or rheumatoid patients. Many other careful laboratory workers have been unable to confirm these findings and the number of the negative results seems to be on the increase. Chapman and his associates,[9] after what seems to have been careful research, consider that "an

analysis of the theoretical basis for and the practical tests of serologic and immunologic reactions which have been proposed for determining which organisms have invaded the tissues of a particular person suspected of having chronic infection indicates that each method is subject to error."

In a recent article Reimann and Havens[32] even question the reliability of the focal infection theory itself. They point out the fact that patients suffering from chronic rheumatism (especially from atrophic or rheumatoid arthritis) are usually subnormal before the disease begins, or become so as a result of the disease. They believe that the focal infections which may be discoverable, very possibly result from their lowered resistance and, therefore, may be interpreted as effects rather than as causes. The probability is suggested by the frequent disappearance of these foci, if and when, the recovery of, or the remission from, the underlying chronic disease occurs.

From the point of view of an orthopedic surgeon I hope that this informed and considerate article will have a wide circulation. Such a presentation has been long overdue. Seeing more patients in the later rather than in the earlier stages of their disease, I have for many years been made aware that although most of them had had teeth and tonsils and many important internal organs taken away, their arthritis remained and paradoxically often seemed unlike their incomes to have been augmented by their losses. Today there remains little informed opinion to support the belief that either active or slumbering infection plays any leading rôle in the initial etiology of hypertrophic or degenerative joint disease, though any active infection may often make the joint symptoms temporarily more acute in both types.

Gastro-intestinal Factors. Deficiency diets and gastro-intestinal disorders probably have an indirect etiologic connotation because they may fertilize the body soil for a crop of arthritic joints. Holbrook,[21] whose experience has been large and whose observations are keen, reports that the majority of his patients with atrophic or rheumatoid arthritis give a history of gastro-intestinal dysfunction and constipation. They present sigmoids which are frequently redundant and colons which are often tortuous with areas of spasm in an otherwise atonic bowel.

Trauma. Hypertrophic or degenerative joint disease may be said to be often initiated by trauma and in both this disease and in atrophic or rheumatoid arthritis, macro- and especially the microtraumata of use are among the chief causes of increase of troubles.

Bauer and Bennett,[3] after many years of research into the nature of hypertrophic or degenerative joint disease, have been led to believe that it results from the wear and tear of increasing age and repeated trauma and is not the result of an inflammatory process, metabolic process or endocrine dysfunction. Because articular

cartilage has little or no power of regeneration they believe that this type of chronic rheumatism can never be completely "cured," but that certain measures may be instituted which will either arrest or slow the progress of the degenerative changes. They recognize the fact that extensive degenerative changes can be present in an individual without necessarily causing any important joint symptoms.

Possible Endocrine Factors. We shall discuss later these newer etiologic possibilities and merely mention them here.

Emotional Etiologic Factors. Every keen experienced student of chronic rheumatism from Charcot[10] to Cobb[11] has been made aware of the possibility of neurologic and psychologic etiologic factors as predisposing and possibly precipitating causes of atrophic or rheumatoid arthritis. Cobb, Bauer and Whiting,[11] writing in 1939, conclude that "environmental stress, especially poverty, grief and family worry, seem to bear more than a chance relationship to the onset and exacerbation of rheumatoid arthritis." This investigation was carefully controlled and included a considerable consecutive series of cases. For many years we have been made conscious of the existence of these etiologic factors, and believe that closest attention should be given them, especially since Cannon has been able to connect emotional disturbances intimately with both functional disturbances of the body systems and with eventual organic lesions. Lucretius Titus Carus,[7] in the last century, B.C., was aware of this emotional factor and of its organic possibilities.

> "Then be it ours with steady mind to clasp
> The purport of the skies, the laws behind
> The wandering courses of the sun and moon;
> To scan the powers that speed all life below;
> But most to see with reasonable eyes
> Of what the mind of what the soul is made
> And what it is so terrible that breaks
> On us asleep or waking in disease."

The Etiologic X Factor. Before we leave the subject of etiology we must refer to perhaps the most important of all etiologic concepts. This is the unknown factor which we know exists but which we have thus far been unable to discover. The chances are better that it will prove to be a biochemical rather than a bacterial factor. For many decades it has been occasionally observed that when certain patients affected by atrophic or rheumatoid arthritis had an attack of jaundice, their joint symptoms frequently almost completely disappeared, very rarely permanently, but often for periods of many weeks or months. It has been known for many years also that when a woman with atrophic or rheumatoid arthritis becomes pregnant, both her objective and subjective joint symptoms markedly improve, to return usually in more aggravated form shortly after

she is delivered. A similar but less impressive train of events often follows a surgical operation and even a simple ether anesthesia.

As far as we are aware, no such remissions occur under such circumstances in the course of hypertrophic or degenerative joint disease. Hench[19] suggests that there may be a factor common to these occurrences in jaundice and pregnancy. Closely related are such diverse substances as cholesterol (which increases during pregnancy), ergosterol (the precursor of vitamin D), some of the sex hormones, cortin and bile acids. All these substances contain the phenanthrene nucleus.

So far we do not have the answer to the question, why do remissions of symptoms in atrophic or rheumatoid arthritis occur often with jaundice and almost always during pregnancy? We may be reckless enough to venture certain guesses before concluding the paper. At present we stand "at attention" before the mystery, "looking and listening," but the train of events which will bring us the good news of discovery is still on the way and alas, behind time.

Therapeutic Trends. Generalized disease: One therapeutic trend overshadows, we may say dominates, all others. It is based on the conviction that chronic rheumatism is a generalized disease analogous to lues, tuberculosis, "Bright's disease." It is not a disease of the joints *per se*, although the joints become diseased.

1. General Measures. *Early Recognition.* Successful therapy demands early recognition and early treatment.

Team Play. We emphasize the importance of "team play." A competent and interested internist is the first essential. He must be the captain of the patient's fate and chart his course, but since the conservation of joint function is a prime desideratum, a knowledgeable bone and joint specialist should be his first mate. Other mates may be required, and physical therapists and perhaps psychiatrists, but they must all be "mates" under one captain.

Rest. Rest of body and mind is another essential. This does not mean inactivity, indeed it often means more exercise, in order to conserve joint function and avoid emotional strain.

Body Mechanics. I must give testimony to the faith that is in me with a few words on the subject of body mechanics as a universally applicable method of the general treatment of a generalized disease. No sculptor or painter ever successfully portrayed a healthy or efficient person who did not exhibit in either activity or repose good body mechanics, or a weak depressed person who did not exhibit faulty posture. William James, the psychologist, once said that the erect posture exerted an important effect upon the emotions. We might have expected this great student of the mind to have said that the emotions exert great influence upon posture, which is to some extent true, but he did not. If we see to it that our rheumatic patients lie and sit and walk in such a manner that the great systems of the body, respiratory, gastro-intestinal, muscu-

lar and skeletal, may function with the smallest amount of mechanical restriction, we shall remove one of the most serious handicaps to their physical and emotional betterment.

2. SPECIFIC MEASURES. *Diet.* There is no standard diet for chronic rheumatism. As Minot has said, we must seek to find the optimum diet for each individual, optimum in caloric value, in quality and in vitamins. Pemberton[29] has destroyed Haige's shibboleth of the proscription of meat and has demonstrated that a diet high in proteins, fat and vitamins and low in carbohydrates very often tends to represent an optimum diet.

There has been much healthy "debunking" of "constipation," yet we must not neglect obviously faulty alimentation, represented perhaps quite as frequently by too rapid passage of food as by intestinal stasis. I am old-fashioned enough still to believe that it is as important to make sure that the ashes of the food we eat do not contain too many clinkers as it is to keep the cylinders of our motor cars free from carbon.

We shall perhaps need soon a little "debunking" of vitamin "cure alls." Articles have appeared stressing the importance of vitamin D and there has been more or less "drug house" urge to employ massive doses, but Abrams and Bauer,[1a] after careful trial and observation, have concluded that the use of large doses of vitamin D in the treatment of atrophic or rheumatoid arthritis is of little or no value and that there is insufficient proof that massive doses may not be harmful. Recent reports suggest that the various vitamin B compounds may have a wider application in very considerably larger dosage than they have been often administered. We know how important adequate amounts of vitamin A and vitamin C have been proved to be.

Vaccines and Sera. The widely accepted theory of focal infection as an important etiologic factor has led to the common employment of vaccine therapy. End-result studies have been disturbingly confusing. It is perhaps fair to say that the reports of their therapeutic value have become less "rosy" in direct ratio to the carefulness of investigation. The recent paper of Sidel and Abrams,[34] read at the 1939 meeting of the American Rheumatism Association, entitled "Treatment of Chronic Arthritis—Results of Vaccine Therapy With Saline Injections Used as Controls," casts grave doubts as to the specific nature of the method. A very considerable number of cases of both atrophic or rheumatoid arthritis and of hypertrophic or degenerative joint disease were included in their studies which seem to have been very carefully controlled. Their conclusions may be summarized by saying that judged by objective and subjective improvement in the condition of the joints and in enhanced ability to work, the injections of vaccines were of no more therapeutic value than the injections of normal saline solution.

Drugs. Since we have no specific drug for chronic rheumatism, we may group the ones in most common use under the old-fashioned headings of sedatives, analgesics, vasodilators and certain drugs which are thought to be useful but the exact action of which we do not know, *e. g.*, sulphur and the salts of gold. It is needless to name the sedatives. These are well known and different physicians have different favorites. The safest analgesics still seem to be the new and old salicylate preparations which are also vasodilators. The more definitely vasodilating drugs such as erythrol-tetranitrate and arsenic, which is thought to influence favorably not only the blood flow but the nature of the blood itself, are often beneficial in the hands of a wise internist who employs them with caution as a whip and spur. The influence, if any, of the formerly frequently prescribed iodides is probably due to their stimulation of thyroid activity.

The knell of the much publicized treatment of chronic rheumatism by sulphur seems to have been rung by the investigations of Freyberg, Block and Fromer[15] and the studies of Abrams and Bauer.[16] The conclusions from both these very thorough and well controlled pieces of research are almost identical to the effect that there is no evidence to suggest that a sulphur deficiency or any abnormality of sulphur metabolism exists in patients with arthritis and that there is no biochemical or metabolic indication of need for, or benefit from, sulphur medication in the treatment of arthritis.

There is more to be said for gold therapy, popularized by Forestier,[14] although as far as we are aware the only well-controlled and to some extent end-result study of the administration of gold salts which has been published is that of Ellman and Lawrence[13] published in 1938. There is much literature on the subject. Hartfall, Garland and Goldie[18] in 1937 reported very favorable results of gold therapy administered to 900 cases of atrophic or rheumatoid arthritis. Nearly 10% they described as "cured" and nearly 57% as greatly improved. We should here remember Kalmeter's end-result studies of cases treated in the Rheumatic Clinics of Sweden without the use of gold, which showed 60% of the patients back on their old jobs and 18% requiring no more pensions when reviewed 3 years after they had been discharged from the hospitals. In the Ellman and Lawrence series, numbering 52 cases, only typical cases of atrophic or rheumatoid arthritis, whose ages ranged from 18 to 68 years were selected. The control group of 20 received intramuscular injections of bland almond oil; the second group of 16 received injections of small doses of Solganol B; the third group of 16 received larger doses of Solganol B. The dangers were recognized and patients with existing kidney damage were excluded. Their results after 9 months' study and two courses of gold therapy are interesting and suggestive.

Of the control group of 20, 1 lost all signs of the disease and 13

were improved; none became worse. Of the group of 16 receiving small doses of gold salts, 6 lost all signs of the disease, 8 were improved, but 1 became worse. Of the group of 16 receiving large doses of gold salts, 8 lost all signs of the disease and 7 were improved, but 1 became worse. The changes in the sedimentation rate were striking. A normal sedimentation rate was attained in 28% of the controls, in 43% of the group receiving small doses of gold and in 72% of the group receiving large doses.

On the other side of the ledger stands the record of toxic reactions. One fatal case occurred in the gold series from agranulocytosis associated with purpura hemorrhagica and in 43% of the cases treated with gold a stomatitis occurred, which in 4 of the gold-treated cases was very severe, very persistent and very painful. In over 18% of the gold-treated cases squamous and exfoliative skin eruptions occurred and were lengthy and resistant to treatment. Even after such a careful, informed and judicial clinical study as this, it is hard to assay the value of this newer form of antirheumatic therapy. It has its seeming triumphs and its possible disasters. We have no exact knowledge as to why it should do good or how it does it. I think it is fair to say that if it be carefully controlled, the opinion seems to be growing that gold therapy has a better chance to survive than either sulphur or vaccine therapy.

Endocrine Products. There is some suggestive evidence (to be presented later) that we may find in certain endocrine extracts and hormones very useful therapeutic agents for the alleviation of certain types of chronic rheumatism.

Climate. Holbrook's[21] study of the incidence of chronic rheumatism among the population of the high and dry Arizona Desert and of some of the western Indian tribes suggests that we must accept the fact that elevation and dryness and sun exert at least a strongly inhibiting influence upon the incidence of atrophic or rheumatoid arthritis.

Physical Therapy. This is perhaps the oldest of the rheumatic "cures." It remains a powerful arrow in the quiver of therapy. I am convinced that it should be planned and supervised and frequently checked, not by a physical therapy technician but by the captain of the patient's fate himself. Otherwise grievous sins may be committed in its name.

Reconstructive Surgery. There remains, and probably always will remain, a certain number of sufferers from chronic rheumatism the fires of whose disease seem to have burnt out leaving them crippled to the point of almost complete disability. I speak from experience when I say that we may rehabilitate to varying but quite worthwhile degrees these pathetic individuals and that we owe them such surgical reconstruction. Wilson and the writer[40] have tried to emphasize the importance of such attempts and to describe the conditions which must obtain to warrant the hope of success.

Before we leave the subject of the therapy of chronic rheumatism, may I say that although we possess no specific curative agent for either of the great types of unknown etiology, we are enthusiastic and not depressed by the results of treatment of the chronic rheumatic diseases by application of the knowledge we now possess. I believe from such statistics as Kalmeter has given us and from the follow-up of private practice, we may expect a certain number of cures, a certain number of remissions, a lesser number of exacerbations and an almost negligible number of patients who will not admit that our care has lightened their load.

Social Approach to the Problem of Chronic Rheumatism. The problem of chronic disease in general has become more serious as the percentage of life expectancy has risen and will apparently continue to rise for many years. The increase of chronic disease is greatest after the age of 45. Two other facts should prick our social and

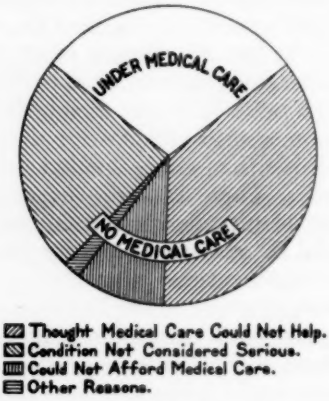


CHART 3.

medical consciences. The findings of the Massachusetts Survey[45] revealed the incidence of chronic disease to be nearly twice as high among the poor as among the well-to-do. This fact is of serious social import. Medically, we should be chagrined, if not alarmed, to realize that four-fifths of the poor and one-half of the well-to-do who were suffering from chronic disease were not under the care of any physician. These findings are a challenge to social service and no less to the medical profession.

The first approach to this social problem would seem to be a change in the education of medical students. Unless they can be made more aware of the incidence of chronic disease and of the methods of approach and treatment we cannot expect to solve the social problem.

Our next social approach would seem to be the establishment of hospitals (not of almshouses) for the study and treatment of chronic

disease. We are of the opinion that the time is ripe for the establishment of separate departments in large general hospitals or of several large hospitals of this character, in many of the great cities, because of the notable recent increase in the number of outstanding physicians who have acquired an acute scientific and humanitarian interest in the chronic rheumatic diseases. These institutions will be expensive to erect, equip and conduct. If philanthropy fails, I believe municipal, state or even Federal financial help should be sought and can be cogently argued for on the grounds of economy alone, but only if there exist in a given community a sufficient number of highly trained physicians acutely interested in helping to solve the medical and social problems which the chronic rheumatic diseases present.

The Look Ahead. I shall attempt in closing to hazard a look into the future, an attempt always dangerous, but the obvious approach to the study of a disease is to proceed from the known to the unknown.

We know that "chronic rheumatism" includes not one but many diseases. We know that trauma, infection, chemical or metabolic disturbances can cause injury to the joints which present varied pathologic patterns. The picture will depend upon the nature of the injurious agent and upon the intensity and duration of its action. The pathologic pictures resulting from causes of known origin, however, are by no means always distinguishable from pathologic pictures the exact causes of which are unknown. This should not surprise us since we know that the tissues of the joints have the power of reacting in only a limited number of ways to various types of insult.

As clinicians we must be aware of the existence of the different types of chronic rheumatism. It is easy to assume that the sole cause of hypertrophic or degenerative joint disease is senescence plus gross or slight functional trauma. The blood may show only a mild anemia and yet the patient may improve both symptomatically and functionally under a therapy of vitamin B complex by mouth and by injections of liver extract.

A second group represents what for lack of a better name we may call arthralgia. My colleague, Dr. Hall,[16] has studied a series of 85 patients in whom for various reasons an artificial menopause had been produced and who had been free from articular or muscular disturbances before castration. Seventy-five per cent of these patients believed that they were suffering from arthritis, but the usual causes for arthritis could not be found. Sometimes joints and muscles were tender to pressure; sometimes joint motions were limited and painful; sometimes the blood sedimentation rate was elevated. They resembled patients with early atrophic or rheumatoid arthritis, complaining of morning stiffness and often of swelling of the joints. Indeed he was unable to make a definite diagnosis.

Before we leave the subject of the therapy of chronic rheumatism, may I say that although we possess no specific curative agent for either of the great types of unknown etiology, we are enthusiastic and not depressed by the results of treatment of the chronic rheumatic diseases by application of the knowledge we now possess. I believe from such statistics as Kalmeter has given us and from the follow-up of private practice, we may expect a certain number of cures, a certain number of remissions, a lesser number of exacerbations and an almost negligible number of patients who will not admit that our care has lightened their load.

Social Approach to the Problem of Chronic Rheumatism. The problem of chronic disease in general has become more serious as the percentage of life expectancy has risen and will apparently continue to rise for many years. The increase of chronic disease is greatest after the age of 45. Two other facts should prick our social and

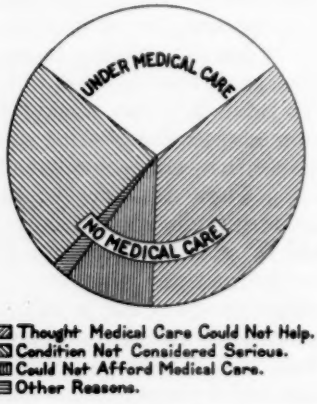


CHART 3.

medical consciences. The findings of the Massachusetts Survey[45] revealed the incidence of chronic disease to be nearly twice as high among the poor as among the well-to-do. This fact is of serious social import. Medically, we should be chagrined, if not alarmed, to realize that four-fifths of the poor and one-half of the well-to-do who were suffering from chronic disease were not under the care of any physician. These findings are a challenge to social service and no less to the medical profession.

The first approach to this social problem would seem to be a change in the education of medical students. Unless they can be made more aware of the incidence of chronic disease and of the methods of approach and treatment we cannot expect to solve the social problem.

Our next social approach would seem to be the establishment of hospitals (not of almshouses) for the study and treatment of chronic

disease. We are of the opinion that the time is ripe for the establishment of separate departments in large general hospitals or of several large hospitals of this character, in many of the great cities, because of the notable recent increase in the number of outstanding physicians who have acquired an acute scientific and humanitarian interest in the chronic rheumatic diseases. These institutions will be expensive to erect, equip and conduct. If philanthropy fails, I believe municipal, state or even Federal financial help should be sought and can be cogently argued for on the grounds of economy alone, but only if there exist in a given community a sufficient number of highly trained physicians acutely interested in helping to solve the medical and social problems which the chronic rheumatic diseases present.

The Look Ahead. I shall attempt in closing to hazard a look into the future, an attempt always dangerous, but the obvious approach to the study of a disease is to proceed from the known to the unknown.

We know that "chronic rheumatism" includes not one but many diseases. We know that trauma, infection, chemical or metabolic disturbances can cause injury to the joints which present varied pathologic patterns. The picture will depend upon the nature of the injurious agent and upon the intensity and duration of its action. The pathologic pictures resulting from causes of known origin, however, are by no means always distinguishable from pathologic pictures the exact causes of which are unknown. This should not surprise us since we know that the tissues of the joints have the power of reacting in only a limited number of ways to various types of insult.

As clinicians we must be aware of the existence of the different types of chronic rheumatism. It is easy to assume that the sole cause of hypertrophic or degenerative joint disease is senescence plus gross or slight functional trauma. The blood may show only a mild anemia and yet the patient may improve both symptomatically and functionally under a therapy of vitamin B complex by mouth and by injections of liver extract.

A second group represents what for lack of a better name we may call arthralgia. My colleague, Dr. Hall,[16] has studied a series of 85 patients in whom for various reasons an artificial menopause had been produced and who had been free from articular or muscular disturbances before castration. Seventy-five per cent of these patients believed that they were suffering from arthritis, but the usual causes for arthritis could not be found. Sometimes joints and muscles were tender to pressure; sometimes joint motions were limited and painful; sometimes the blood sedimentation rate was elevated. They resembled patients with early atrophic or rheumatoid arthritis, complaining of morning stiffness and often of swelling of the joints. Indeed he was unable to make a definite diagnosis.

He decided to observe them carefully and administer estrogenic therapy. The results of treatment with the ovarian hormones were often quick and dramatic. The evidence suggested increased vulnerability of the muscles and joints.

Certain suggestive observations have been made on several younger women complaining of arthralgia who possessed low stamina, small breasts and whose menstrual flow was painful and scanty. He suspected an ovarian deficiency. One of these young women whose malady had been diagnosed as rheumatic fever has been followed now for 3 years and her symptoms are quite well controlled by this form of therapy. A married woman of 28 sought consultation during the fourth week of her third attack of what had been called infectious arthritis. Each attack had been preceded by an acute upper respiratory infection and in the two previous attacks she had been confined to her bed for 3 and 6 months. Examination showed slightly limited motion in both hips and knees and tenderness to pressure over both the knee and finger joints. No foci of infection could be found, the electrocardiogram was normal, and the sedimentation index was high, 1.0. Otherwise the physical examination was negative. The history revealed very scanty, painful, disabling menstruation which had led her to submit to an exploratory pelvic operation and a division of the pubic nerve. Under large doses of estrogenic substance she was free from symptoms in 2 weeks. What appears to happen when an infection strikes a person with ovarian gland deficiency may well happen when an infection occurs in a patient with a food deficiency, let us say of vitamin B. It is interesting that McCarrison,[22] writing years ago on food deficiency, expressed his opinion that such a sequence of events takes place.

In discussing hypertrophic arthritis or degenerative joint disease you may remember that we confessed to a little doubt in our minds as to whether in all cases senescence and wear and tear, important as they are, were always the *only* important etiologic factors. One more clinical case will illustrate why our minds are still open.

We have followed for 8 years a patient of over 50 years, seen first because of an almost crippling affection of the right hip joint, a typical *malum coxæ senilis* or degenerative joint disease. The left hip also was very slightly involved. She has been coöperative in every way. She has worked assiduously on prescribed general and special exercises looking to the correction of faulty body mechanics and exercises for the affected leg in particular. Because of a suspected lack she has been given considerable quantities of estrogenic material. The joint motion has increased in all ranges, especially in internal rotation which in our experience rarely returns when lost. Muscle spasm has disappeared.

I refer again to the dramatic and sometimes complete remission of the symptoms of atrophic or rheumatoid arthritis associated with

severe jaundice and pregnancy. If we can find the substance produced in the body which is responsible for these remissions we might hope to approach an important etiologic agent. No endocrine disturbance has yet been proved to be the sole cause of any type of chronic rheumatism. The rationale of an endocrine lead, however, is suggested by the following considerations:

We know that pregnancy may cause true remission of atrophic or rheumatoid arthritis. If we could reproduce the biochemical conditions of pregnancy or if we should find that patients who suffer from this disease frequently lack some substance present in the pregnant woman, we might be able to arrest the disease and approach a specific therapy.

From our present knowledge the major hormone increase in pregnancy is the estrogenic hormone, for during pregnancy the placenta manufactures huge quantities of the hormone. The absence of this hormone may explain the frequency of joint disturbances at the menopause, said to represent 24% in a study of 1000 women.[23] Its absence may also explain why women are prone to develop arthritis after miscarriage and after pregnancy and lactation.

It must be remembered that at least two things may happen after castration: *a*, removal of ovarian hormones from the body; and, *b*, resulting overactivity of the anterior pituitary gland which floods the body with pituitary hormones. Young[41] and others have shown that overactivity of the pituitary hormones may damage the pancreas and produce diabetes. We know that it may damage the gonads as in acromegaly. Do these facts not justify us in wondering whether excess of anterior pituitary excretion may not damage the joint structures also? Irradiation of the pituitary by Roentgen ray seems to relieve disturbances associated with the true menopause and the administration of estrogenic substance has the same effect.

It is possible that the administration of estrogenic substance may prove to be an important form of replacement therapy in arthritis and that it may put a brake on anterior pituitary excretion.

There are two pieces of suggestive evidence in this connection. Putnam[31] and his associates, in producing in dogs experimental acromegaly in 1928 by the administration of pituitary substance, found at necropsy not only enlarged bones but osteophytes on their prominences and on the patella and what may be still more suggestive, separate flakes of bone lying in the anterior ligament of the spine. Putnam and Davidoff,[30] in later work on acromegaly in 1936, report finding osteophytes indistinguishable from those seen in hypertrophic arthritis or degenerative joint disease extending into tendons and ligaments and sometimes fastening several vertebræ together.

The other piece of suggestive evidence has been furnished by the

work of the two Silberbergs, M. and R.[35] I quote from their article, "A Comparison of the Effects of Anterior Pituitary on Skeletal Tissues of Young and Adult Guinea Pigs": "The severe arthropathic changes which were produced by the anterior pituitary hormone in old (mature) animals are comparable to those taking place in 'arthritis deformans' in man." By the term "arthritis deformans" I fancy they are referring to hypertrophic arthritis or degenerative joint disease.

I have no conviction that either the exact etiology or the rational treatment of atrophic or rheumatoid arthritis or of hypertrophic or degenerative joint disease has been found. These findings in experimental animals and a small amount of clinical work merely suggest that more intensive and extensive clinical and laboratory research along these lines should be encouraged.

I desire to acknowledge that in the preparation of this paper I have received generous help from my friend and medical colleague, Dr. Francis C. Hall. He is a much better rheumatologist than I, because as an internist his breadth of view is wider.

REFERENCES.

(1.) **Abrams, N. R.**, and **Bauer, W.**: (*a*) J. Am. Med. Assn., **3**, 1632, 1938; (*b*) New England J. Med., **222**, 541, 1940. (2.) **Allison, N.**, and **Ghormley, R. K.**: Diagnosis in Joint Disease, New York, William Wood & Co., 1931. (3.) **Bauer, W.**, and **Bennett, G. A.**: J. Bone and Joint Surg., **18**, 1, 1936. (4.) **Bigelow, G. H.**, and **Lombard, H. L.**: (*a*) New England J. Med., **203**, 1232, 1930; (*b*) Cancer and Other Chronic Diseases in Massachusetts, Boston, Houghton, Mifflin Company, p. 19, 1933. (5.) **Billings, F.**: Focal Infection, the Lane Medical Lectures, California, Stanford Univ. Press, 1916. (6.) **Burbank, R.**, and **Hadjopoulos, L. G.**: J. Am. Med. Assn., **84**, 637, 1925. (7.) **Lucretius Titus Carus**: De Rerum Natura. (8.) **Cecil, R. L.**, **Nicholls, E. E.**, and **Stainsby, W. J.**: (*a*) Arch. Int. Med., **43**, 571, 1929; (*b*) Am. J. Med. Sci., **181**, 12, 1931. (9.) **Chapman, W. B.**, **Berens, C.**, **Lieb, C. W.**, **Rawls, W. B.**, and **Stiles, M. H.**: Am. J. Clin. Path., **9**, 500, 1939. (10.) **Charcot, J. M.**: Primary Progressive Chronic Articular Rheumatism, Paris, Paris theses, 1853. (11.) **Cobb, S.**, **Bauer, W.**, and **Whiting, I.**: J. Am. Med. Assn., **113**, 668, 1939. (12.) **Dawson, M. H.**, **Olmstead, M.**, and **Boots, R. H.**: J. Immunol., **23**, 187, 205, 1932. (13.) **Ellman, P.**, and **Lawrence, J. S.**: Gold Therapy in Rheumatoid Arthritis: An Assessment of Its Value with Control Experiments. Reports on Chronic Rheumatism, No. 4, New York, The Macmillan Company, p. 121, 1938. (14.) **Forestier, J.**: Lancet, **1**, 441, 1932. (15.) **Freyberg, R. H.**, **Block, W. D.**, and **Fromer, M. F.**: J. Clin. Invest., **19**, 423, 1940. (16.) **Hall, F. C.**: New England J. Med., **219**, 1015, 1938. (17.) **Goldthwait, J. E.**, **Painter, C. F.**, and **Osgood, R. B.**: Preliminary Report of a Series of Metabolic Observations Made in Atrophic Arthritis, Hypertrophic Arthritis, Osteitis Deformans, and the Normal, Philadelphia, American Medicine, **5**, **7**, 547, 590, 1904. (18.) **Hartfall, S. G.**, **Garland, H. G.**, and **Goldie, W.**: Lancet, **2**, 784, 1937. (19.) **Hench, P. S.**: J. Am. Med. Assn., **109**, 1481, 1937. (20.) **Hench, P. S.**, **Bauer, W.**, **Dawson, M. H.**, **Hall, F. C.**, **Holbrook, P. W.**, and **Key, J. A.**: Ann. Int. Med., **12**, 1006, 1939. (21.) **Holbrook, W. P.**: Ibid., **7**, 457, 1933. (22.) **McCarrison, R.**: Studies in Deficiency Disease, London, Henry Frowde and Hodder & Stoughton, pp. 45, 234, 1921. (23.) Medical Women's Federation: Report of Subcommittee of Council, Lancet, **1**, 106, 1933. (24.) **Moody, R.**: Paleopathology, Chap. V., Urbana, Ill., University of Illinois Press, 1923. (25.) National Health Survey: Report of the Surgeon-General of Public Health, Washington, D. C., Govt. Printing Office, No. 6, p. 19, 1935–1936. (26.) **Nichols, E. H.**, and **Richardson, F. L.**: J. Med. Res., **16**, 149, 1909. (27.) **Nicholls, E. E.**, and **Stainsby, W. J.**: J. Clin. Invest., **10**, 323, 1931. (28.) **Pemberton, R.**: Arthritis and Rheumatoid Conditions—Their Nature and Treatment, Philadelphia, Lea & Febiger, 1929. (29.) **Pemberton, R.**, and **Osgood, R. B.**: The Medical and Orthopaedic Management of Chronic Arthritis, New York, The Macmillan Company, Chap. IX, p. 213, 1934.

(30.) **Putnam, T. J.**, and **Davidoff, L. M.**: Proc. Assn. for Res. in Neur. and Ment. Dis., **17**, 716, 1936. (31.) **Putnam, T. J., Benedict, E. B.**, and **Teel, H. M.**: Arch. Surg., **18**, 1708, 1929. (32.) **Reimann, H. A.**, and **Havens, W. P.**: J. Am. Med. Assn., **114**, 1, 1940. (33.) **Ruffer, M. A.**: Studies in the Paleopathology of Egypt, Chicago, University of Chicago Press, 1926. (34.) **Sidel, N.**, and **Abrams, M. I.**: J. Am. Med. Assn., **114**, 1740, 1940. (35.) **Silberberg, M.**, and **Silberberg, R.**: Am. J. Path., **15**, 557, 1939. (36.) **Small, J. C.**: Med. Clin. North America, **13**, 857, 1930; **15**, 427, 1931. (37.) **Smith, G. E.**, and **Jones, F. W.**: Archaeological Survey of Nubia, Cairo, Cairo Natl. Print. Dept., 1910. (38.) **Strangeways, T. S. P.**: Lancet, **2**, 628, 1918. (39.) **Tillett, W. S., Abernethy, T. J.**, and **Fisher, A. M.**: J. Clin. Invest., **11**, 810, 1932. (40.) **Wilson, P. D.**, and **Osgood, R. B.**: New England J. Med., **209**, 117, 1933. (41.) **Young, F. G.**: Lancet, **2**, 372, 1937.

"TARGET CELL" ANEMIA.

ANERYTHROBLASTIC TYPE OF COOLEY'S ERYTHROBLASTIC ANEMIA.*

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INVESTIGATION of the case of an Italian youth of 20 who presented anemia and splenomegaly revealed a peculiar abnormality of the erythrocytes and a generalized disturbance of the bones. Many of the red cells presented a "bull's eye" or "target" appearance; the bones showed thickening and an unusual "honeycomb" appearance. In addition a large tumor originating from one of the ribs and involving the right lung was discovered. Since an outstanding abnormality was the presence of large numbers of peculiar erythrocytes designated as "target cells" by Barrett,[3] the name "target cell anemia" was adopted for this previously undescribed condition. Although no nucleated red cells were present in the peripheral blood, the possibility that the condition might be a *forme fruste* or an anerythroblastic type of Cooley's anemia was considered. The report which follows is based upon a preliminary study of the case.†

Case Report. Joseph C., aged 20, of Italian parentage, was referred by Dr. I. M. Blumerfield on May 5, 1939. He had no complaints. In the course of a visit to another member of the family, the doctor had noticed the boy's yellowish pallor. On examination in March, 1939, splenomegaly was discovered and blood studies revealed a hypochromic anemia (Hgb. 43%, R.B.C. 2.45 million). After 3 weeks of treatment with ferrous sulphate (12 gr. daily) the hemoglobin rose to 55% and the erythrocyte count to 3.39 million. Because of the persistent splenomegaly, further study was considered desirable.

The patient was born in Boston of Italian (Sicilian) parentage. His father and mother were alive and well. One sister and 3 brothers were well; 1 sister was "queer" and "dropped things;" 1 brother was a mental defective. Examination of the family revealed no icterus, anemia, or other hematologic abnormalities except in the well sister, who had a slight hypo-

* Aided by a grant from the Charlton Fund of Tufts College Medical School.

† An abstract of this article appeared in the Bull. New England Med. Center, **2**, 101, 1940.

chromic anemia and 3.4% of target cells (see below). The "queer" sister was found to have athetoid movements of the hands, arms, and legs, and the diagnosis of Wilson's disease (lenticular degeneration) was made by a neurologist. No evidences of anemia, hepatic insufficiency, or of bone disturbance were present.

In 1925, at the age of 5, the patient had been studied at another hospital, where he had been admitted because of fever. Full records of this hospital admission were fortunately available. Physical examination disclosed marked pallor, large injected tonsils, a somewhat enlarged heart with a systolic murmur diffusely heard over the precordium, and an enlarged spleen which was felt 3 to 4 cm. below the left costal margin. The hematologic findings were as follows: Hgb. 42% (Sahli), R.B.C. 2.60 million, W.B.C. 10,200, platelets 216,000 (direct method), reticulocytes 7%; sodium chloride fragility test: hemolysis began at 0.475—complete at 0.275; differential count: P. 54, L. 39, M. 2, B. 4, E. 1; the red cells showed slight to moderate achromia, anisocytosis and poikilocytosis; no nucleated red cells

FIG. 1.—J. C., an Italian boy, aged 20, with "target cell anemia"—anerythroblastic type of Cooley's erythroblastic anemia. There is no definite Mongoloid appearance of the face.

were observed. Other laboratory findings, including blood cultures, were negative. While in the hospital, there was improvement in the anemia. A definite diagnosis was not made after 5 weeks of study, although the possibility of Hanot's cirrhosis was considered. Roentgen rays of the bones were not taken. The patient was discharged (against advice) with the diagnosis of acute pharyngitis and ? Hanot's cirrhosis.

Since then, except for a tendency to underweight, the patient had felt well. The family had noticed yellowish pallor for about 2 years. In the past year he had gained 17 pounds in weight (from 125 to 142 pounds). After graduation from high school, he had performed occasional clerical jobs, but was usually unemployed. Except for smoking a few cigarettes daily, he had no unusual habits. He was extremely uncoöperative regarding investigation, so that repeated studies were difficult to obtain. He refused hospitalization.

Physical examination in May, 1939, revealed a well-developed, rather tall, somewhat pale, slightly icteric young man. He looked typically

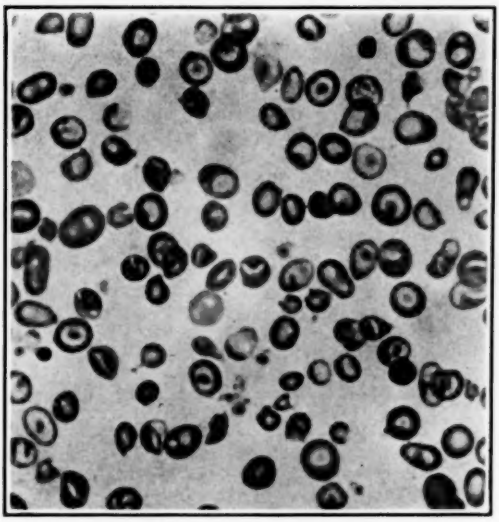

FIG. 2.—Stained blood smear (×560). Note the great diversity in size and shape of the red cells and the large number of "target cells."

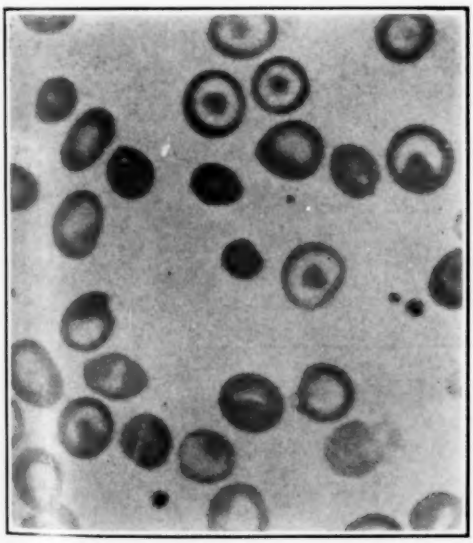

FIG. 3

FIG. 4

FIG. 3.—Stained blood smear (×1000). Typical "bull's eye" or "target cell" forms are seen, together with some having "bridges" between the "eye" and the periphery of the erythrocyte.

FIG. 4.—Fresh, unstained, unmodified preparation of blood. Note the very thin cells seen on end, the tendency of these cells to buckle and to form cup-shapes, and so on, and the impaired rouleaux formation due to diversity in erythrocytic configuration.

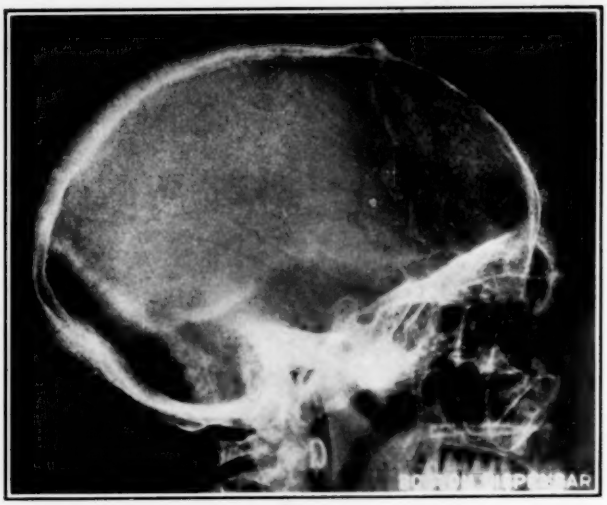

Fig. 6

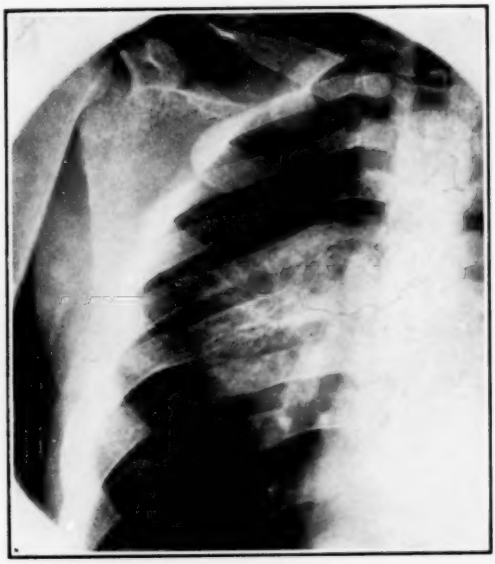

Fig. 7

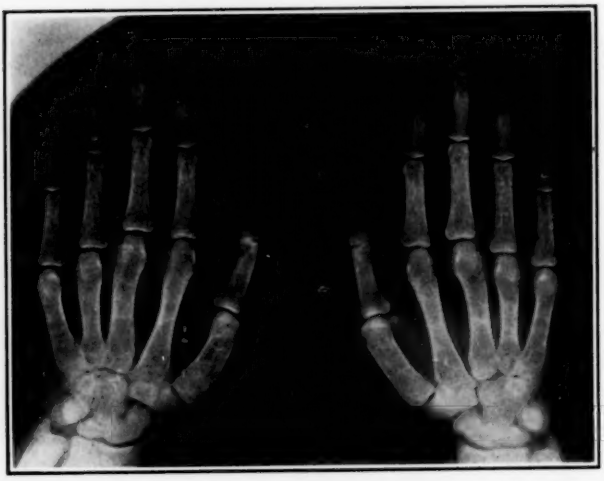

Fig. 8

"Italian" and did not then present Mongoloid features. However, in December, 1939, when anemia was more pronounced, he presented a well-marked Mongoloid appearance, perhaps due to the greater icterus and pallor at that time. The heart was not enlarged; a loud, blowing systolic murmur was present at the apex and along the left border of the sternum; no presystolic or diastolic murmurs were heard. The liver dullness was not increased and the liver edge was not palpable. The spleen was readily felt 3 to 4 finger breadths below the left costal margin. There were no "spider" telangiectases. The remainder of the examination was negative.

TABLE 1.—JOSEPH C. LABORATORY DATA.

	March, 1939.	$FeSO_4$, 1.0 gm./d., March-May.	May, 1939.	No treatment.	December, 1939.
Hgb. (Evelyn) 100% 15.6 gm.	43	..	67	..	50
Erythrocytes	2.45	..	4.28	..	3.12
Leukocytes	..	..	6100	..	5200
Platelets	..	..	560,000	..	1,051,000
Reticulocytes (%)	..	..	0.9	..	5.1
Target cells (%)	..	..	26	..	32
Hematocrit (%)	..	..	35	..	25
M.C.V.* (cu. micra)	..	..	81	..	80
M.C.D.* (micra)	..	..	7.6	..	7.4
M.C.T.* (micra)	..	..	1.8	..	1.85
M.C.H.* (micro-microgm.)	..	..	24.5	..	25
M.C.H.C.* (%)	..	..	30	..	31
Fragility (saline)	..	..	.42–.04	..	.44–.04
Bilirubin (mg.)	..	..	1.9–2.4	..	2.4
Calcium (mg.)	..	..	..	..	10.7
Phosphorus (mg.)	..	..	..	..	3.8–4.5
Phosphatase (Bodansky units)	..	..	..	..	2.0
Cholesterol: Total	..	..	124	..	74
Esters	..	..	..	..	54

* These initials indicate mean corpuscular volume, diameter, thickness, hemoglobin and hemoglobin concentration, respectively.

The laboratory data were as follows: *Urine:* no albumin, sugar, or bilirubin; the urobilinogen content was 1 to 20 (Wallace and Diamond). *Stool:* dark brown in color; the daily fecal urobilinogen output (Watson method) was 890 mg. *Blood chemistry:* icterus index 20, 22.5; bilirubin (indirect type) 1.9, 2.4 mg. per 100 cc.; serum calcium 10.7; phosphorus 3.8, 4.5; alkaline phosphatase 2 Bodansky units, total cholesterol 75 and 125 mg., cholesterol esters 54 mg. The bromsulphalein liver function test showed 6% retention of the dye at the end of 30 minutes (normal). Negative Kahn and Hinton tests of the blood serum. *Hematology:* (see Table 1)

LEGENDS FOR FIGS. 6, 7 AND 8.

FIG. 6.—Roentgen film of skull. Note the thickening of the diploë and the diffuse "honeycomb" appearance.

FIG. 7.—Roentgen ray of the chest demonstrated a large tumor composed of bone and soft tissue, probably hyperplastic bone-marrow, together with partial destruction of the 6th rib.

FIG. 8.—Roentgen rays of the hands showed striking osteoporotic changes, particularly of the metacarpal bones. Similar changes were demonstrated in all the other bones.

this showed a hypochromic type of anemia with some tendency to leukopenia and granulocytopenia. In March, 1939, when the anemia was slight, the mean corpuscular volume was 81 cu. micra, the mean cell diameter 7.6 micra, and the mean cell thickness 1.8 micra (normal approximately 2 micra in our series). The data for mean corpuscular volume and cell thickness were essentially unchanged when the anemia was more pronounced in December, 1939. The fragility test showed greatly *increased resistance* to hypotonic salt solutions: hemolysis commenced at 0.42 to 0.40% and was incomplete at 0.04% (normal controls: beginning hemolysis 0.44 to 0.46—complete hemolysis 0.24 to 0.22). In 0.3% solution of sodium chloride, approximately 33% of the cells were "resistant" (*i. e.*, unhemolyzed). The outstanding feature of the blood smear was the presence of large numbers of typical target cells as described by Barrett and as confirmed by us in such conditions as severe hepatic disease, following splenectomy, and in sickle-cell anemia. The percentage of typical target cells varied from 26 to 33% of the total red cells.

Target Cells. The typical target cell in stained preparations is shaped like a bull's eye, with a peripheral ring of hemoglobin separated by a clear unstained zone from a dense central "eye." This characteristic appearance of the target cell is modified in other cells, in which a "bridge" of hemoglobin is seen between the peripheral and central masses of hemoglobin. Various gradations between the typical target cell and those with "bridges" may be noted.

TABLE 2.—C. FAMILY. HEMATOLOGIC DATA.

	Anna (mother).	Orazio (father).	George.	Tony.	Lucy.	Mary.
Hemoglobin	..	..	..	..	87	68
Erythrocytes	..	..	..	..	4.36	4.72
Leukocytes	..	..	..	..	5700	6600
Reticulocytes (%)	0.5	0.5	0.2	0.3	0.2	2.4
Target cells (%)	0.0	Rare	0.0	0.0	0.0	3.4
Hematocrit (%)	..	..	..	..	42	35
M.C.V. (cu. micra)	..	..	..	..	96	74
Fragility (saline)	..	..	..	..	.42-.24	.42-.16
Bilirubin (mg. per 100 cc.)	..	..	..	..	0.5	

The differing appearances of the target cells may be explained, as Barrett points out, by assuming for the cell a central thickening, like that of a squat collar-button. When viewed on end, this cell would have the appearance of a Mexican hat, as Haden has suggested. Viewed from above at different levels these cells present either a bull's eye appearance or show bridged forms.

Differential Price-Jones diameter counts in our case revealed that the target cells were larger than the average red cell in the same preparations. Whereas the average red cell diameter for all the red cells was 7.6 micra, that of the target cells was 8.6 micra. This finding is quite in contrast with that of Barrett in a case of obstructive jaundice in which he found that the diameter of target cells was smaller (7.6 micra) than that of the average red cell (8.04). This difference can probably be explained on differences in the two types of cases since the case described by Barrett was probably one of macrocytic anemia (of hepatic disease), whereas our case presented a diminished mean corpuscular volume.

In fresh preparations, the cells formed rather poor rouleaux, composed of cells which varied greatly in their configuration. Isolated cells appeared

definitely thinner and more flexible than normal, changing shape readily. Cells viewed on end not infrequently presented a bulging of the central mass of hemoglobin apparently due to buckling of the unusually thin cell. Cup-shaped forms were commonly seen. When viewed from above these cells usually presented a very distinct circular appearance with at times a suggestion of bull's eye appearance. This could be accentuated by placing the preparation somewhat out of focus.

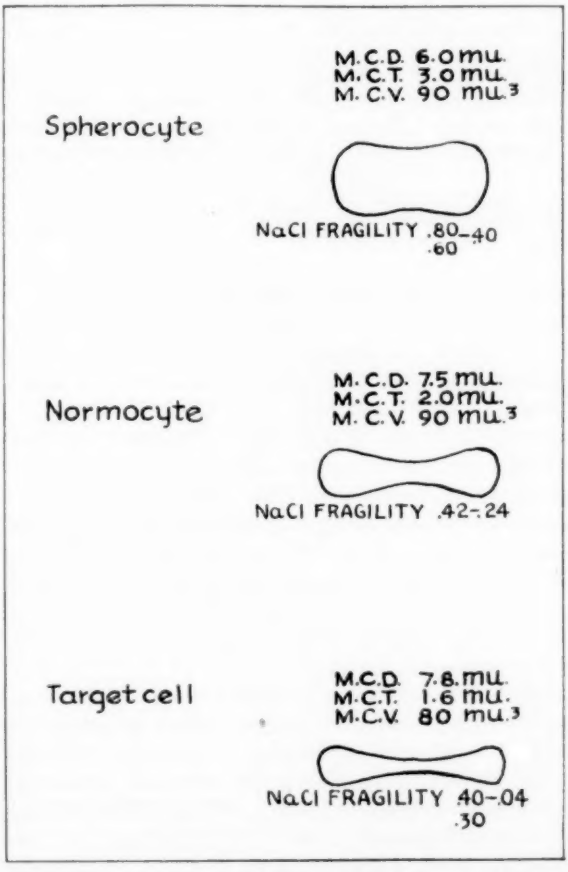

FIG. 5.—Representation of some of the physical differences between the normal red cell, the thick spherocyte, and the thin target cell. The thinner the red cell, the more resistant is it to hypotonic hemolysis.

Roentgen Ray Findings. The unusual nature of the Roentgen ray findings was not at first suspected but was fortunately discovered when films of the esophagus for varices were requested. The latter were negative. Films of the chest showed a large tumor of bony structure, irregularly trabeculated, oval in shape, measuring 9 by 8 by 8 cm. and occupying the medial and posterior portion of the right upper lung field. In the region of this mass, the sixth rib posteriorly was destroyed, particularly in its

medial aspect, to about 6 cm. from its vertebral articulation. All the ribs, the clavicles, the scapulæ, and the humeri showed numerous irregular areas of increased radiance with coarse irregular trabeculations. Roentgen rays of the skull showed great thickening of the inner and outer tables with the same honeycomb appearance. All the facial bones, including the jaw, were involved. The bones of the pelvis, the thighs, the hands, and feet were similarly affected in greater or less degree, the metacarpal bones showing the most striking osteoporotic changes. Flat plates of the abdomen showed marked enlargement of the spleen, the lower border extending below the level of the crest of the ilium, and from the lateral aspect of the abdomen to almost the left border of the spine.

Bone-marrow Biopsy. Sternal puncture revealed one of the most cellular marrows ever obtained in our experience. The ratio of nucleated red cells to white cells was 4 to 1 (normal in puncture preparations about 0.5 to 1). Differential count of 500 cells showed: erythrogones 6.4%, normoblasts A 9.6%, normoblasts B 32%, normoblasts C 35%, myeloblasts 1.6%, myelocytes 5.4%, metamyelocytes 7.6%, mature polymorphs. 2.4%, histiocytes 0.6%. The erythroblastic cells contained in general very small amounts of cytoplasm.

Comment. 1. *Target Cells.* Although the only extensive studies of this unusual type of red blood corpuscle have been made by Barrett,[3] they were first described as a special type of erythrocyte by Haden and Evans.[12] The latter authors refer to them as "dimpled corpuscles" and liken their form to that of a Mexican hat. They state: "One occasionally sees a few cells of this shape in other anemias, but they are never present in any significant number except in sickle cell anemia." This statement has been criticized by Barrett, with whom we can agree that the target cell is found in significant numbers in some cases of obstructive jaundice and severe hepatitis, in some cases of hypochromic anemia, and following splenectomy. In addition, we have (for the first time) demonstrated substantial and at times large numbers of these cells in Cooley's erythroblastic anemia.

Our studies* of the target cell confirm those of Barrett. The cell is abnormally thin, tends to "buckle" and to present in stained preparations a bull's eye appearance. In contradistinction to the thick spherocyte, the target cells are unusually resistant to hypotonic solutions of sodium chloride. When these cells are present in any significant number (over 4%) they result in a lengthening of the fragility span, with complete hemolysis occurring between 0.16 and 0.02%, depending upon the number of these cells present. In the case described, hemolysis was incomplete at a concentration of sodium chloride of 0.04%. Examination of the centrifuged red cells from concentrations of sodium chloride below 0.30%, following resuspension in the patient's own (heparinized) plasma demonstrated the high concentration of target cells. When the red cells were suspended in varying concentrations of hypotonic solutions of

* To be published.

sodium chloride and the hematocrits determined, the following figures were obtained:

Concentration of NaCl solution.	Hematocrit (%).	Mean corpuscular volume (cu. micra).
Unmodified (in isotonic oxalate) solution	25	80
.80	30	96
.72	32	102
.60	34	109
.40	40	128
.30	45	144

Traces of hemolysis were present in the 0.40 and 0.30 concentrations of sodium chloride solution. Before moderate hemolysis occurred (below the concentration of 0.30%), the cells had almost doubled in volume, thus indicating their unusual capacity for taking up water before hemolysis resulted (Haden[11]).

The target cell may be said to be the antithesis of the spherocyte. Haden,[11] and Castle and Daland[7] concluded that the thick cells of hemolytic jaundice were unusually fragile to hypotonic salt solutions because less swelling was required to rupture an almost spherical cell than one with a discoidal form. As the result of experimental studies on hemolytic anemia, Dameshek and Schwartz[10] concluded that the spherocyte was a red cell which had been damaged by a hemolytic agent with consequent loss of the normal biconcave shape. A completely spherical cell, representing the greatest damage by hemolysin, bursts even in solutions of salt only slightly hypotonic (0.84 to 0.76). At the other extreme, the cell which is unusually thin can absorb a large quantity of fluid before it finally reaches the bursting stage, or complete hemolysis. The abnormally thin target cell is thus able to withstand hemolysis at exceedingly low concentrations of sodium chloride.

2. *"Target Cell Anemia" and Related States.* The criticism may be made that there is insufficient justification for the use of the designation of "target cell anemia" in the case here presented. It is conceded that this designation tends to focus attention on an abnormality which is perhaps not fundamental, but that other abnormalities (such as those relating to the spleen or the marrow) may be of greater importance. However, the same criticism may be made for the nomenclature in use for most states associated with anemia, *i. e.*, pernicious anemia, hypochromic anemia, and aplastic anemia. Sufficient precedent for this type of designation exists, moreover, in the conditions known as sickle cell anemia, erythroblastic anemia, erythroblastosis of the newborn and so on. Until it is possible to classify all types of anemia on an etiologic basis, the retention of such graphic terms is probably justifiable, providing one realizes that the designation used represents only one feature of some more fundamental abnormality.

Target cell anemia may be closely related to or indeed even a phase of the condition known as erythroblastic or Mediterranean

anemia. Certain similarities are evident: the racial factor (Italian in our case); the somewhat Mongoloid appearance; the hypochromic anemia with splenomegaly; the increased resistance of the red cells to hypotonic salt solutions; the bilirubinemia; and the well-marked and generalized bone changes with great thickening of the skull. Because of these similarities, we investigated the blood picture of a few cases of Cooley's anemia.* In all of these, target cells in variable number were found, very large numbers being present in 1 splenectomized case. Lehndorff,[14] in his monographic article on Cooley's anemia, describes these cells without, however, further designating them; excellent illustrations of the various types of abnormal erythrocytes are given in the colored plate of his article.

Certain differences may be pointed out between our case and those of erythroblastic anemia:[4,8a,9] 1, the boy was fundamentally in fair health at the age of 20 (this is exceptional in Cooley's anemia); 2, he had a hypochromic anemia which responded well to the administration of iron; this does not ordinarily occur in Cooley's anemia; 3, no nucleated red cells were found in the blood smears either in 1925 at the age of 5 or in 1939 at the age of 20; the term "erythroblastic anemia" indicates that the outstanding feature is the presence of numbers of nucleated red cells; 4, the Roentgen ray appearances of the bones differed slightly (but not fundamentally) from those in Cooley's anemia, *i. e.*, there was no "hair-brush" effect in the Roentgen rays of the skull, and according to two roentgenologists, the appearance of the bony trabeculations differed somewhat from that of Cooley's anemia.† The finding of a bony tumor encroaching on the lung is a unique observation.

These differences may be merely superficial. The boy might have had erythroblastic anemia as an infant and might have quickly "outgrown" it. (No nucleated red cells were, however, present at the age of 5.) The lack of nucleated red cells in the blood might be indicative of either complete recovery, a more or less "spent" state, or of a latent or *forme fruste* condition. The exceedingly hyperplastic marrow picture might have the same relationship to an "anerythroblastic" picture as the marrow crowded with myeloblasts has to an "aleukemic" blood picture with leukopenia and absence of primitive cells. The slight differences in the bone changes from the typical cases of early childhood might be on the basis of growth and gradual change in the bone picture.

The target cell and its relation to Cooley's erythroblastic anemia may be looked upon from another, and perhaps more fundamental aspect. That is, the basic abnormality in Cooley's anemia might not be the nucleated red blood cell, which indeed is non-specific since erythroblastosis occurs in many conditions, but the target cell.

* We are indebted to Drs. Louis K. Diamond of the Children's Hospital, and James M. Baty of the Boston Floating Hospital for their coöperation.

† We are indebted to Drs. Alice Ettinger, Pratt Diagnostic Hospital; Samuel A. Robins, Beth Israel Hospital; George M. Wyatt, Children's Hospital; E. C. Vogt and Felix Fleischner for their examinations of the roentgenograms and their interpretations.

This cell, which is unusually resistant to hypotonic solutions of NaCl, might be the result of an hereditary defect of red cell production in the bone-marrow, with or without relationship to a splenic abnormality. The extremely hyperplastic bone-marrow, which results in the well-known osteoporotic changes, is ordinarily reflected by erythroblastosis in the peripheral blood, but it is conceivable, as in the case here presented, that in certain so-called latent cases, target cells and not erythroblasts may dominate the blood picture.

Caffey,[5] in his review of the roentgenologic changes in Cooley's anemia, observes that certain cases show the long bone changes yet lack the characteristic thickening and linear striations of the skull. He believes that certain mild cases probably reach adulthood and might even transmit the disease.* This speculation is placed on firm foundation by the work of Caminopetros[6] who demonstrated that certain non-affected members of families with cases of the disease showed an increased resistance of the red cells to hypotonic solutions of salt. This leads to the definite possibility that the target cell is the inherited factor responsible for the disease known, in its full-blown state, as Cooley's erythroblastic anemia.

The coëxistence of the resistant target cells with a hemolytic tendency as manifested by "indirect" bilirubinemia and an increased output of urobilinogen in the feces may at first glance appear somewhat paradoxical. This feature, together with the lack of response to splenectomy in both Cooley's and sickle cell anemia are quite in contrast with those of the "typical" hemolytic anemias in which spherocytosis, increased fragility and dramatic response to splenectomy are common, and may indicate possible relationships between the former condition. Although the red cells of erythroblastic anemia, sickle cell anemia, and target cell anemia are *more* resistant to solutions of hypotonic sodium chloride *in vitro*, it is possible that they may be *less* resistant to breakdown *in vivo*, with resultant evidences of increased hemolysis.

Bone changes are common in Cooley's anemia, but similar changes are occasionally found in sickle cell anemia and (to less extent) in congenital hemolytic jaundice.[8b] They probably represent a greatly expanded marrow cavity in the presence of extreme hyperplasia. The bone changes in our case are probably explicable on the same basis. The tumor arising from one of the ribs, composed in part of relatively soft-appearing tissue and in part of bone, probably represents a large mass of ectopic bone-marrow which has resulted from great expansion due to unusual hyperplasia.

Summary. In an Italian youth with hypochromic anemia, splenomegaly, and a hemolytic type of icterus, unusual changes were discovered in the red blood cells and the bones. About a third of the red cells presented the appearance of "targets" or "bull's eyes;" these cells were unusually resistant to hypotonic solutions of sodium chloride. No nucleated red cells were present. Generalized osteo-

* Eight cases have been reported in individuals over the age of 14.[1,2,6,8c,13,15,16]

porotic changes with great thickening of the skull were present; in addition a bony tumor arising from a rib encroached on the right upper lung. Target cells have been described in sickle cell anemia, cirrhosis of the liver, chronic hypochromic anemia after splenectomy, and in other conditions. The present studies have shown that they are also common in Cooley's erythroblastic anemia.

The condition of "target cell anemia" as described in this paper may be a *forme fruste*, an anerythroblastic type of Cooley's erythroblastic anemia or a closely related condition. The possibility is broached that Cooley's anemia, sickle cell anemia, and target cell anemia are related conditions with target cells and increased saline resistance as common denominators. In Cooley's anemia, the target cell is probably a more fundamental abnormality than the erythroblast, and may represent the basic hereditary defect. In these atypical hemolytic states, a lack of response to splenectomy further differentiates them from most cases of congenital and acquired hemolytic icterus.*

REFERENCES.

(1.) **Allen, E. G.**, and **Childs, D. S.**: New York State J. Med., **36**, 641, 1936. (2.) **Atkinson, D. W.**: Am. J. Med. Sci., **198**, 376, 1939. (3.) **Barrett, A. M.**: J. Path. and Bact., **46**, 603, 1938. (4.) **Baty, J. M.**, **Blackfan, K. D.**, and **Diamond, L. K.**: Am. J. Dis. Child., **43**, 667, 1932. (5.) **Caffey, J.**: Am. J. Roentgenol., **37**, 293, 1937. (6.) **Caminopetros, J.**: Ann. de méd., **43**, 27, 104, 1938. (7.) **Castle, W. B.**, and **Daland, G. A.**: Arch. Int. Med., **60**, 949, 1937. (8.) **Cooley, T. B.**: (*a*) Am. J. Dis. Child., **33**, 786, 1927; (*b*) Ibid., **36**, 1257, 1928; (*c*) Brennermann's Practice of Pediatrics, Hagerstown, W. F. Prior Company, vol. **3**, Chap. 16, 1937. (9.) **Cooley, T. B.**, and **Lee, P.**: Trans. Am. Pediat. Soc., **37**, 29, 1925. (10.) **Dameshek, W.**, and **Schwartz, S. O.**: Am. J. Med. Sci., **196**, 769, 1938. (11.) **Haden, R. L.**: The Nature of Hemolytic Anemia. Symposium on the Blood and Blood-forming Organs, Madison, Univ. of Wisconsin Press, 1939. (12.) **Haden, R. L.**, and **Evans, F. D.**: Arch. Int. Med., **60**, 133, 1937. (13.) **Kramer, B.**: Quoted by Thalheimer, E. J., *et al.*[16] (14.) **Lehndorff, H.**: Ergebn. d. inn. Med. u. Kinderh. **50**, 568, 1936. (15.) **Mandeville, F. B.**: Radiology, **15**, 72, 1930. (16.) **Thalheimer, E. J.**, **Mezetti, A.**, and **Gershon-Cohen, J.**: J. Pediat., **14**, 349, 1939.

ANEMIA AND WATER RETENTION.

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Edema is of common occurrence in anemic patients. Addison in 1855[1] describing the anemia which now bears his name, wrote

* The very interesting paper of Wintrobe, Matthews, Pollack, and Dobyns (Jour. Am. Med. Assn., **114**, 1530, 1940) appeared while the present article was in press. The identical disorder is described as "A Familial Hemopoietic Disorder in Italian Adolescents and Adults resembling Mediterranean Disease (Thalheimer)". The authors of this paper, which is based on a more extensive material, bring out substantially, the same findings as our own.

"some slight œdema is probably perceived about the ankles." This edema, at one time ascribed to cardiac weakness, and more recently attributed to a concomitant lowering of the plasma protein level, has been shown to occur independently of the latter.[6,7,9] Peters and Eisenman[9] suggest that "some characteristic of the condition of anemia itself tends to facilitate the appearance of edema." Schade, Claussen and Birner[10] found that, at a given perfusion pressure, whole blood tended to withdraw more fluid from the surrounding medium than did its own serum. These observations, however, as pointed out by Peters and Eisenman[9] were made with biologically inert collodion membranes, not subject to nutritive disturbances which might alter capillary permeability.

The presence or absence of edema, and its magnitude, when present, is a matter of clinical judgment. There is no way that the amount of edema present at any one observation can be quantitatively measured in any but the most crude manner. It is a well-known fact that patients with heart disease who have fairly extensive dependent edema at night may awaken in the morning with little or no evident edema, but without change in body weight, indicating that a redistribution of the edema fluid has concealed its presence. Similarly, patients with "nephrotic" edema may shift this fluid during the day so that eyelids almost closed with edema on awakening are normal in the evening. It has further been shown that some individuals may retain as much as 5 or more kilograms of water without showing manifest edema whereas others will reveal as little as one kilogram of retained fluid with pitting edema.

In a previous study of water retention and edema formation in pregnancy[11] it was found that one could measure the "tendency to edema" by observing the changes in body weight which occur within a relatively short period of time following the administration or withdrawal of sodium salts. In pregnant women it was found that, in the absence of anemia, the percentage increase in body weight following the administration of sodium salts could be correlated in linear fashion with the colloid osmotic pressure of the plasma proteins. It was therefore decided to make similar observations on non-pregnant patients with varying degrees of anemia.

Methods. Thirty-two observations made on 26 patients will be discussed first (Table 1). Nine patients had pernicious anemia in mild relapse while under inadequate treatment. Eight patients had hypochromic anemia, 2 associated with chronic blood loss due to carcinoma of the stomach, 1 associated with the Plummer-Vinson syndrome, 1 with metrorrhagia, 1 with pellagra and 3 due to chronic blood loss from hemorrhoids. Six patients had anemia secondary to acute blood loss, in 1 case epistaxis, and in the remaining 5 instances due to peptic ulcer. These 14 patients were not studied until at least 1 week after bleeding had ceased. There were also studied 3 patients without anemia, 2 of whom were convalescent from acute respiratory infections, and 1 with peptic ulcer.

All patients were ambulatory on the hospital ward. They were permitted fluids *ad libitum* and partook of ward diets. They were weighed at the same time each morning. Blood for hemoglobin and plasma protein determina-

tions was withdrawn without stasis from an antecubital vein after the patients had been at rest for twenty minutes or more. Venous pressure determinations were made on 11 patients by the method of Moritz and von Tabora.[8] Plasma protein values were determined by a micro-modification of Howe's technique.[5] The colloid osmotic pressure was calculated from the values for plasma albumin and globulin by the use of the nomogram of Wells, Youmans and Miller.[13] The patients were observed during a preliminary period of 3 or 4 days until their weights were stabilized. Then each one received daily for 10 days in divided doses, either 23 gm. of sodium bicarbonate or (in 2 cases only) 16 gm. of sodium chloride, containing the same amount of sodium as the larger dose of bicarbonate.

Results. The venous pressure, determined on 11 patients, was 3.0, 3.5, 4.5, 5.0, 6.0, 6.0, 7.5, 7.5, 8.0, 10.0, and 10.5 cm. of water, all of which are within the normal range.

The hemoglobin determinations varied from 30 to 94% of 15.6 gm. per 100 cc. (Table 1). The calculated colloid osmotic pressure of the plasma proteins varied from 63 to 98% of 300 mm. of water. These values, 15.6 gm. per 100 cc. for hemoglobin and 300 mm. of water for osmotic pressure, have been considered normal in this clinic. The lack of correlation between hemoglobin and osmotic pressure is apparent from Chart 1. The coefficient of correlation is 0.3786 with P= 0.05.* The 2 patients who had both low plasma protein osmotic pressures and low hemoglobin values were suffering from carcinoma of the stomach with cachexia and pellagra, respectively. If these 2 are eliminated the coefficient of correlation drops to 0.2391 with P = >0.1, an entire absence of significant correlation.

The maximum amount of water retained within a period of 10 days following the administration of sodium as measured by the weight gains varied from 0.8 to 10.8% of original body weight (Table 1). This maximum gain generally occurred by the sixth or seventh day after sodium administration was commenced. In many instances slight to moderate spontaneous diuresis occurred subsequently while sodium administration was continued as has been noted before.[11] In 12 of the 32 observations pitting edema was present at the time of the maximum water retention. In the patient who gained 10.8% of his original body weight this extended as high as the abdominal wall and râles were heard in both lower lungs. Following the withdrawal of sodium the râles and the edema disappeared.

The percentage of weight gain has been plotted against the plasma protein osmotic pressure in Chart 2. Slight if any correlation is apparent. The coefficient of correlation is 0.4990 with P = 0.01. In contrast to this the correlation between the weight gain and the hemoglobin is quite apparent in Chart 3. The coefficient of correlation is 0.7780 with P = 0.01, a highly significant correlation.

Since, in non-anemic patients there is a good correlation between weight gain and plasma protein osmotic pressure, an endeavor was made to correlate the weight gains in these patients with anemia with both plasma protein osmotic pressure and hemoglobin level.

* Probability coefficient.

TABLE 1.—BLOOD LEVELS, PLASMA PROTEIN VALUES AND WEIGHT GAINS IN 32 OBSERVATIONS MADE ON 26 PATIENTS RECEIVING SODIUM SALTS.

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Case No.	Sex.	Age.	R.B.C. (millions per c.mm.).	Hg. (% of 15.6 gm. per 100 cc.).	Total protein (gm. per 100 cc.).	Plasma albumin (gm. per 100 cc.).	Calculated colloid osmotic pressure (mm. H_2O).	Weight gain in % of original body weight.	Day of maximum weight gain.	Manifest edema.	Diagnoses.
1	M	80	3.51	30	6.0	3.0	235	10.8	10	+++	Hypochromic anemia due to chronic blood loss from carcinoma of stomach.
2	M	72	2.31	31	5.0	2.7	188	7.6	3	++	Hypochromic anemia due to chronic blood loss from carcinoma of stomach.
3	M	54	2.35	35	5.0	2.9	192	6.4	3	+	Hypochromic anemia; chronic alcoholism; pellagra.
4	M	53	1.65	37	5.6	3.8	245	4.6	9	0	Pernicious anemia.
5	F	76	3.10	38	6.1	3.8	268	9.0	8	++	Hypochromic anemia due to metrorrhagia.
2	M	71	3.73	45	5.7	3.6	243	5.2	9	++	Hypochromic anemia due to chronic blood loss from carcinoma of stomach.
6	F	50	4.03	45	6.5	3.8	287	3.1	9	0	Hypochromic anemia from bleeding hemorrhoids.
7	F	45	3.70	46	6.6	3.8	290	4.1	8	+	Hypochromic anemia from bleeding hemorrhoids.
8	F	49	3.78	48	5.7	3.0	222	6.0	6	+	Anemia from severe epistaxis; hypertension.
9	M	58	3.05	49	5.9	3.3	242	5.5	10	++	Anemia of acute blood loss due to peptic ulcer.
10	M	58	3.80	50	5.7	3.2	230	5.3	6	0	Hypochromic anemia due to bleeding hemorrhoids and malnutrition.
11	F	23	2.45	54	5.6	3.6	240	3.9	5	0	Pernicious anemia.
12	F	56	4.60	55	5.5	3.3	225	7.7	9	++	Idiopathic hypochromic anemia with Plummer-Vinson syndrome.
13	M	59	2.94	55	5.8	3.6	250	3.4	6	0	Anemia of acute blood loss due to peptic ulcer.
14	F	53	3.43	58	5.6	3.5	240	4.0	9	0	Anemia of acute blood loss due to peptic ulcer; hypertension.
15	F	50	3.01	59	6.2	3.7	268	4.5	5	+	Pernicious anemia.
16	M	36	3.19	59	5.2	3.5	220	3.4	9	0	Anemia of acute blood loss due to peptic ulcer.
17	M	31	3.58	60	6.0	3.4	250	2.6	9	0	Anemia of acute blood loss due to peptic ulcer.
4	M	53	3.33	60	5.6	4.1	255	1.3	5	0	Pernicious anemia.
8	F	49	4.18	68	6.4	3.7	277	4.4	7	0	Anemia from severe epistaxis; hypertension.
18	M	58	2.92	68	6.4	3.9	287	3.0	4	0	Pernicious anemia.
10	M	58	4.80	70	5.9	3.3	245	2.9	8	0	Hypochromic anemia due to bleeding hemorrhoids and malnutrition.
19	F	30	2.81	70	5.8	4.0	262	2.1	3	0	Pernicious anemia.
20	F	71	3.18	71	6.7	3.7	292	2.8	7	0	Pernicious anemia.
14	F	53	4.60	73	6.5	4.0	295	1.4	8	0	Anemia of acute blood loss due to peptic ulcer; hypertension.
21	F	64	2.70	73	6.2	3.8	275	1.4	7	+	Pernicious anemia.
22	M	41	3.96	76	6.3	4.3	295	1.6	4	0	Pernicious anemia.
23	M	60	4.02	78	6.0	2.9	235	2.5	4	+	Convalescent pneumonia.
10	M	58	5.31	80	6.2	3.5	260	1.3	8	0	Hypochromic anemia due to bleeding hemorrhoids and malnutrition.
24	F	57	2.99	80	6.0	4.2	280	1.2	7	0	Pernicious anemia.
25	F	53	5.27	88	5.7	3.2	230	0.8	4	0	Convalescent respiratory infection.
26	M	54	5.32	94	5.7	3.4	240	2.2	6	0	Peptic ulcer without blood loss.

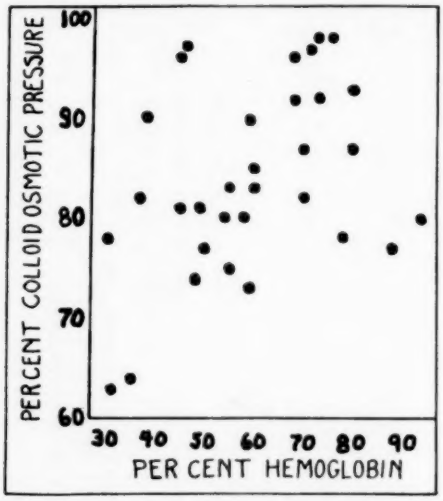

CHART 1.—The relationship of colloid osmotic pressure of the plasma proteins to the hemoglobin level. (In this and subsequent charts the hemoglobin is expressed in per cent of 15.6 gm. per 100 cc., and the colloid osmotic pressure in per cent of 300 mm. H_2O.) Correlation coefficient 0.3786. P = 0.05.

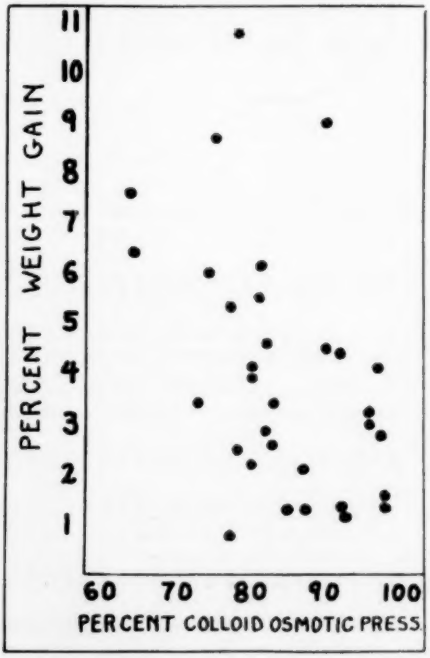

CHART 2.—The relationship of body weight gain resulting from sodium administration and the colloid osmotic pressure of the plasma proteins. Correlation coefficient 0.4990. P = 0.01.

Various formulæ were tried. One of these is shown in Chart 4, where weight gain is plotted against the product of osmotic pressure and hemoglobin. The coefficient of correlation is 0.7863 with P = 0.01, a value not significantly different from that obtained with hemoglobin alone, the probable error of the difference between these two correlation coefficients, being greater than their difference.

In addition to the above studies observations have been made on 7 additional patients. Three of these, with untreated pernicious anemia in severe relapse, received sodium bicarbonate in the same fashion as noted above. Two showed an actual loss of weight during

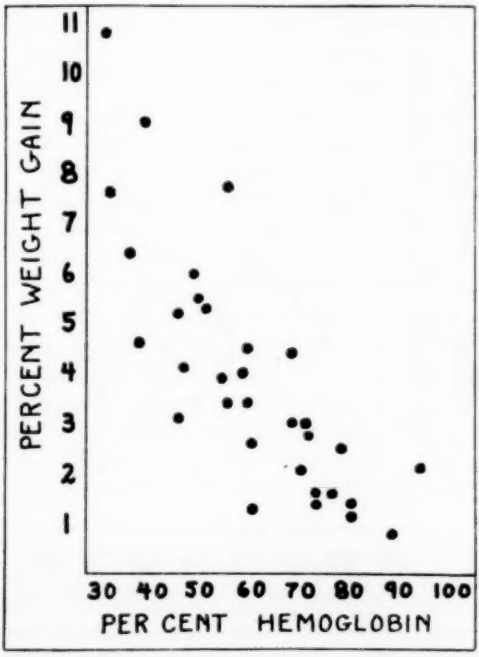

CHART 3.—The relationship of body weight gain resulting from sodium administration and the hemoglobin level. Correlation coefficient 0.7780. P = 0.01.

the administration of sodium, and the third failed to show any significant gain. All 3, however, showed significant water retention following the institution of liver therapy.

One patient with severe hypochromic anemia failed to show any weight gain while sodium was being administered but promptly lost 2% of her original weight when sodium was omitted.

Two patients with hypochromic anemia received 40 gm. of sodium bicarbonate daily. Each retained much more water than patients with similar blood levels receiving 23 gm. of sodium bicarbonate.

A patient who had gained 2% of weight while taking soda lost

this amount of weight during a period of 24 hours when he was kept flat in bed, regaining it upon again becoming ambulatory. This observation was repeated on the same patient with identical results.

One of the 26 patients reported who had hypochromic anemia associated with nutritional deficiency received 50 mg. of thiamin chloride daily by intravenous injection at the time that her water retention from sodium was most marked. The thiamin was without effect upon her weight or edema.

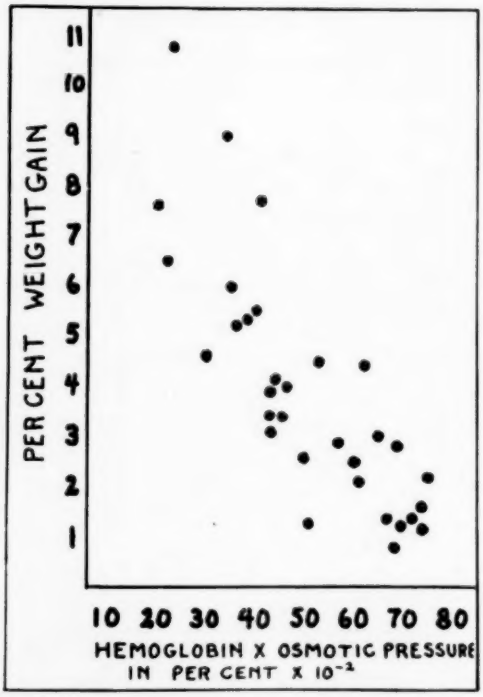

CHART 4.—The relationship of body weight gain resulting from sodium administration and the product of colloid osmotic pressure × hemoglobin × 10^{-2}. Correlation coefficient 0.7863. P = 0.01.

Discussion. Are the weight changes occurring within brief periods of time in the patients described above due to changes in water balance? Hastings, Liu, and Dieuaide[4] have shown that the difference between the total fluid intake (water + water in food + water of combustion of food) and the total fluid loss (urine + water of feces + water lost through lungs + insensible perspiration) closely parallels the difference in day to day weights of animals carefully studied. Gamble[3] has considered weight changes over short periods of time as largely due to changes in water balance, and since it is chiefly the extra-cellular water which is involved, considers that for

each kilogram of body weight gained there is retention of 147 m-eq. of sodium (approximately 4.0 gm. of NaCl per lb. of weight). The improbability of loss or deposition of any quantity of body tissue in these brief periods is a further argument for considering that the weight changes observed are largely due to water and sodium retention.

It is apparent that anemia in these cases did not lead to an elevation of venous pressure. Therefore an increased intracapillary pressure from an increased venous pressure ("cardiac weakness") cannot be responsible for the water retention observed.

There can be no question but that the plasma protein osmotic pressure plays an important rôle in water balance. However, since there was no significant correlation between the plasma protein osmotic pressure and the weight changes in these patients, it appears that lowering of the plasma proteins was not a significant factor. It should be pointed out, however, that none of the patients in this series had extremely low plasma protein values. Only 2 were below 73% of normal, these being 63 and 64% respectively. Had patients been available with very low plasma proteins, there is little doubt but that the influence of these levels would have been apparent.

The velocity of blood flow in anemia has been shown to increase proportionately to the severity of the anemia.[2] In Schade, Claussen and Birner's experiments it was observed that the flow of cell-free serum was two and a half times that of whole blood *when the pressure gradients were equal*. However, in patients with anemia it is conceivable that arteriolar dilatation may occur resulting in higher filtration pressures within the capillaries. No proof of this is available, nor is there any evidence that anemia leads to altered capillary permeability.

It therefore appears that anemia *per se*, through a mechanism which cannot as yet be defined, leads to a tendency to water retention. This tendency is not due to diminished plasma proteins or increased venous pressure.

In addition to the above, the failure of 3 patients with untreated pernicious anemia in severe relapse to exhibit this water retention until after specific therapy for their anemia, must be noted. This is comparable to Vaughan's observation[12] that in 11 of 12 patients with pernicious anemia water retention occurred spontaneously during the period between the institution of treatment and the height of the reticulocyte rise. No explanation is at hand, but it is of interest that this behavior with regard to water and sodium exhibited by patients with Addisonian pernicious anemia is not unlike that shown by patients with Addison's disease of the supra-renal capsules. The commonly observed edema of the early phase of remission in pernicious anemia as well as Vaughan's observations may possibly be ascribed to the specific effect of therapy in restoring normal salt

and water balance as well as to the common increase in salt ingestion consequent on the improved appetite of remission.

Summary and Conclusions. 1. Thirty-two observations have been made on 26 patients whose hemoglobin values varied from 30 to 94%. Water retention was induced in each patient by the administration of sodium salts. The magnitude of this water retention varied inversely with the hemoglobin level, the more anemic subjects showing the greatest retention. This phenomenon was not due to a concomitant lowering of the plasma protein level or to an increase in the venous pressure.

2. An exception to the above was noted in the fact that 3 patients with Addisonian pernicious anemia in severe relapse did not exhibit significant water retention during sodium administration until after the institution of liver therapy.

3. Anemia *per se* appears to be a factor conducive to water retention.

REFERENCES.

(1.) **Addison, T.**: On the Constitutional and Local Effects of Disease of the Supra-Renal Capsules, London, Samuel Highley, 1855. (2.) **Blumgart, H. L.**: Medicine, **10**, 1, 1931. (3.) **Gamble, J. L.**: Communication presented at Boston before the Suffolk District Medical Society, January 31, 1940. (4.) **Hastings, A. B., Liu, S. H.**, and **Dieuaide, F. R.**: J. Clin. Invest., **10**, 683, 1931. (5.) **Howe, P. E.**: J. Biol. Chem., **49**, 109, 1921. (6.) **Keefer, C. S.**, and **Myers, W. K.**: Trans. Assn. Am. Phys., **47**, 231, 1932. (7.) **Meulengracht, E., Iverson, P.**, and **Nakazawa, F.**: Acta med. Scand., Suppl., **26**, 248, 1928. (8.) **Moritz, F.**, and **v. Tabora, D.**: Deutsch. Arch. f. klin. Med., **98**, 475, 1910. (9.) **Peters, J. P.**, and **Eisenman, A. J.**: Am. J. Med. Sci., **186**, 808, 1933. (10.) **Schade, H., Claussen, F.**, and **Birner, M.**: Ztschr. f. klin. Med., **108**, 581, 1928. (11.) **Strauss, M. B.**: Am. J. Med. Sci., **194**, 772, 1937. (12.) **Vaughan, J. M.**: Arch. Int. Med., **47**, 688, 1931. (13.) **Wells, H. S., Youmans, J. B.**, and **Miller, D. G., Jr.**: J. Clin. Invest., **12**, 1103, 1933.

FAILURE TO CONTROL POLYCYTHEMIA RUBRA VERA WITH LIPOCAIC AND CHOLINE.

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Persistent increase in the number of circulating erythrocytes is claimed to have been produced in animals (so-called "experimental polycythemia") by a number of methods. These have included cobalt administration, exposure to reduced oxygen tensions, and exercise. Marshall[4] claimed that injection of certain liver extracts would cause a temporary fall in the erythrocyte level of rats rendered polycythemic by cobalt (but that whole liver feeding exalted the polycythemia). It is maintained by Davis[2a,b,c] that "polycythemias" produced in dogs by the above-mentioned methods can be controlled or prevented by feeding raw liver, by the adminis-

tration of certain liver extracts by mouth and by injection, and also by feeding choline hydrochloride. The "polycythemia" produced by Davis in dogs with cobaltous chloride has been criticized by Brewer[1] as statistically non-significant. Major[3] treated 3 cases of polycythemia rubra vera with highly refined liver extracts over many months and could not demonstrate any effect. Davis suggested that the refined liver extracts employed by Major might not contain the active principle involved in reduction of the erythrocyte count. Experiences in the University of Chicago clinics have not demonstrated the usefulness of certain liver extracts in this disease. However, it has been noted on several occasions that the inception of vigorous liver therapy in cases of subacute combined degeneration of the cord with little or no anemia has been followed by a temporary but significant reduction of the red blood count.

On the basis of Davis' experimental results it was thought worth while to test, in accepted cases of polycythemia rubra vera, the effects of choline hydrochloride, and also of "lipocaiac," the pancreatic hormone shown by Dragstedt and his associates to have certain properties similar to, though far more intense than, choline in lipid metabolism.

Methods. The cases were selected as representing classical instances of polycythemia rubra vera. Six-tenths of a gram of choline hydrochloride daily (divided in 3 doses) was administered as representing a slightly greater dose than that used in dogs by Davis (8 mg. per kilo). This dose administered over approximately 3 weeks caused no subjective symptoms. Over similar periods the dose of lipocaiac was 12 capsules a day of an extract made available for these experiments by the kindness of Dr. Lester Dragstedt. Each capsule contained approximately 10 gr. of lipocaiac, and the dose employed is known to produce a full effect on lipid metabolism. Slight diarrhea was noted, probably due to the content of inorganic sulphates in the preparation; there were no other subjective phenomena.

Case Abstracts. Case 1.—(*Choline hydrochloride.*) E. H., female, aged 56, admitted to Billings Hospital in November, 1937 (Unit No. 185897), complaining of a mass in the left upper quadrant known to be present for 2 years. Examination showed marked facial rubor, moderate clubbing of the fingers, slight proptosis oculi, and marked enlargement of the spleen. Roentgen ray of the chest showed 25% cardiac enlargement.

Clinical diagnosis: Polycythemia rubra vera.

Progress: Patient has been treated constantly with acetyl phenyl hydrazine until period of experiment.

Date, 1937	R.B.C., millions per c.mm.	Hgb., gm. per 100 cc.	Retic., %.	Cell vol.	W.B.C. in thous.	Medication.
10/19	6.130	18.7	4.5	55	19.2	Acetyl phenyl hydrazine
1939						
4/18	..	..	..	..	..	Discontinue acetyl phenyl hydrazine
4/27	5.730	18.0	4.3	49	23.0	Choline hydrochloride, 0.2 gm. t.i.d.
5/ 1	7.300	17.5	7.5	..	17.9	Choline hydrochloride, 0.2 gm. t.i.d.
5/11	6.580	17.7	6.9	..	19.5	Choline hydrochloride, 0.2 gm. t.i.d.
5/16	5.390	15.4	1.3	51	17.0	Choline hydrochloride, 0.2 gm. t.i.d.
5/25	7.370	18.7	3.7	55	20.4	Discontinue choline
6/26	6.370	18.7	2.6	50	21.0	

Case 2.—(*Choline hydrochloride and lipocaiac.*) C. L., female, aged 38, admitted to Billings Hospital in May, 1939 (Unit No. 220362), complaining

of recurrent tingling discomfort in first the left, then the right arm and hand, which had been variously diagnosed as erythromelalgia, Raynaud's disease, and cervical neuritis. Examination showed slight subnutritional state, moderate ocular proptosis, moderate finger clubbing, spleen palpable at the costal margin, and slight enlargement of the liver. Laboratory findings included normal chest Roentgen ray, normal hepatic function tests, B.M.R. +3%, slight reduction in vital capacity.

Clinical diagnosis: Polycythemia rubra vera.

Date, 1939.	R.B.C., millions per c.mm.	Hgb., gm. per 100 cc.	Retic., %.	Cell vol.	W.B.C. in thous.	Medication.
5/15	8.400	20.2	2.0	..	10.4	*Nil*
6/ 5	8.240	20.0	1.5	..	11.8	*Nil*
6/16	7.400	20.0	1.0	..	..	Choline HCl, 0.2 gm. t.i.d.
6/23	7.630	20.0	0.5	..	..	Choline, as above
6/30	6.860	21.0	..	..	..	Choline, as above
7/ 5	6.880	20.0	..	..	..	Choline, as above
7/ 8	..	..	..	..	..	Discontinue choline
9/14	5.140	17.5	1.0	50	9.8	*Nil*
10/ 5	5.850	17.6	0.8	..	12.2	*Nil*
10/19	8.140	22.2	3.0	56.5	8.0	Choline HCl, 0.2 gm. t.i.d.
10/26	7.900	21.4	..	55	..	Choline, as above
11/ 2	7.330	20.4	1.2	54	..	Choline, as above
11/ 9	6.830	19.4	0.8	54	7.6	Choline, as above
11/16	6.770	18.8	..	54	11.0	Choline, as above
11/30	7.620	21.2	1.2	53.5	14.0	Discontinue choline Lipocaiac, cap. XII daily
12/ 7	7.640	20.2	1.2	55	14.8	Lipocaiac, as above
12/14	7.850	19.8	2.4	56	12.5	Lipocaiac, as above
12/21	7.220	19.6	0.8	52	14.4	Lipocaiac, as above
1/ 4	8.250	21.2	..	56	14.6	Discontinue lipocaiac

CASE 3.—(*Choline hydrochloride and lipocaiac.*) H. B., male, aged 36, admitted to Billings Hospital (Unit No. 204906) in August, 1938, with gangrene of the left leg following trauma. Slight finger clubbing, rubor facies, and marked enlargement of the spleen then noted, and count found to be 6.51 millions and 21.2 gm. of hemoglobin. Laboratory examination showed normal Roentgen ray of the chest. Leg amputated and patient treated as polycythemia rubra vera with Fowler's solution.

Clinical diagnosis: Polycythemia rubra vera. Gangrene-thrombosis of left leg.

Date, 1939.	R.B.C., millions per c.mm.	Hgb., gm. per 100 cc.	Retic., %.	Cell vol.	W.B.S. in thous.	Medication.
5/ 2	4.800	17.7	0.83	..	4.20	Discontinue Fowler's
6/13	5.160	17.7	3.2	51	4.80	Choline HCl, 0.2 gm. t.i.d.
6/20	5.000	17.5	1.8	50	..	Choline HCl, 0.2 gm. t.i.d.
6/23	5.330	18.0	..	52	..	Choline HCl, 0.2 gm. t.i.d.
6/25	..	..	..	..	..	Discontinue choline HCl
6/29	5.350	18.0	1.43	51	5.20	*Nil*
9/ 5	5.770	16.5	3.1	48	..	*Nil*
9/12	6.140	18.0	1.1	53	6.60	*Nil*
9/19	6.160	18.7	..	51	4.50	Choline HCl, 0.2 gm. t.i.d.
9/25	5.900	17.9	1.2	54	7.20	Choline HCl, 0.2 gm. t.i.d.
10/ 3	6.100	18.0	..	55	6.20	Choline HCl, 0.2 gm. t.i.d.
10/10	6.260	18.7	2.1	58	..	Choline HCl, 0.2 gm. t.i.d.
10/17	5.820	18.0	3.4	51	8.50	Discontinue choline
10/24	5.840	18.0	..	54	8.90	Lipocaiac, cap. XII daily
10/31	5.870	17.3	2.0	53	9.40	Lipocaiac, cap. XII daily
11/ 7	5.530	19.6	1.8	51.5	7.30	Lipocaiac, cap. XII daily
11/14	5.580	16.2	..	52	..	Lipocaiac, cap. XII daily
11/21	6.400	17.7	..	54	6.80	Lipocaiac, cap. XII daily
11/28	6.760	18.7	2.3	55.5	6.50	Lipocaiac, cap. XII daily
12/ 5	6.400	18.0	..	57	6.40	Discontinue lipocaiac

CASE 4.—(*Lipocaiac.*) P. L., female, aged 48, admitted to the Billings Hospital (Unit No. 177125) in April, 1940, complaining of weakness, tiredness, headaches, and vomiting of 2 years' duration. She had noted recently the ruddiness of her complexion. Examination showed moderate subnutrition, facial rubor, slight finger clubbing, spleen palpable at the costal margin, slight hypertension (146/110), and moderate clinical enlargement of the

heart. Laboratory examination showed faint albuminuria with moderate reduction in renal function to the Van Slyke urea clearance test, B.M.R. +25%, slight reduction in vital capacity. Roentgen ray showed moderate cardiac enlargement with clear pulmonary parenchyma. Sternal biopsy showed hyperplastic bone marrow in all elements, with prominent megakaryocytes. Hepatic functions normal to galactose tolerance test.

Clinical diagnosis: Polycythemia rubra vera: moderate hypertension with slight reduction in renal function for further evaluation. (On hospital bed rest for 7 days, blood pressure dropped to 134/88.)

Date, 1940.	R.B.C., millions per c.mm.	Hgb., gm. per 100 cc.	Retic., %.	Cell vol.	W.B.C. in thous.	Medication.
3/18	7.330	21.2	0.8	68	8.00	*Nil*
3/25	7.070	20.8	1.0	70	..	Lipocaiac, cap. XII daily
3/28	7.420	22.8	0.2	70	..	Lipocaiac, cap. XII daily
4/ 2	7.440	23.0	..	72	8.20	Lipocaiac, cap. XII daily
4/11	8.200	27.0	8.0	74	8.20	Lipocaiac, cap. XII daily
4/25	7.260	22.0	2.5	70	..	Lipocaiac, cap. XII daily
5/ 2	7.140	23.0	1.1	70	8.80	Lipocaiac, cap. XII daily
5/ 9	8.440	26.2	0.09	73	8.90	Discontinue lipocaiac

Conclusions. Lipocaiac and choline hydrochloride were shown to have no effect, in doses believed adequate, on the erythrocyte level in polycythemia rubra vera over periods of up to 1 month.

REFERENCES.

(1.) **Brewer, G.**: Am. J. Physiol., **128**, 345, 1940. (2.) **Davis, J. E.**: (*a*) Ibid., **122**, 397, 1938; (*b*) Proc. Soc. Exp. Biol. and Med., **40**, 445, 1939; (*c*) Am. J. Physiol., **127**, 322, 1939. (3.) **Major, R. H.**: J. Lab. and Clin. Med., **24**, 65, 1938. (4.) **Marshall, L. H.**: Am. J. Physiol., **114**, 194, 1935.

BLOOD PRESSURE DETERMINATIONS BY PATIENTS WITH ESSENTIAL HYPERTENSION.

I. The Difference Between Clinic and Home Readings Before Treatment.*

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The present knowledge of essential hypertension is based on measurements of blood pressure made by physicians, largely in the clinic or office. No data are available regarding the level of blood pressure which obtains during a patient's normal daily activities. The importance of such information for a complete knowledge of the life history of hypertension is evident.

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The present study has been an attempt to compare the blood pressure readings in the office or clinic with those taken at home by the patient or some member of the patient's household. This study has permitted the correlation of the home blood pressure levels with changes in environment, symptoms, weather, season, and so on, and also with treatment. The present paper, the first of a series on these subjects, limits itself chiefly to a report of the differences themselves between the blood pressure readings taken by the physician and those taken at home by the patient or some member of the household, in patients not under treatment.

Material. The present report is a study by the above method of 34 patients with essential hypertension. There were 10 males and 24 females; their ages ranged from 32 to 67 years (average 43). The average known duration of their hypertension by history was 6.2 years, and by hospital records 5 years. The patients were followed by the authors for an average period of 22 months, during which period the 34 patients made an average of 21 visits each to the clinic. At each of these visits the blood pressure was recorded before and during 20-minute rest periods. In all of these patients annual 7-foot heart Roentgen rays, electrocardiograms, and studies of renal function were made. The latter included dilution-concentration tests, routine examinations of single specimens, and intravenous pyelography.

In 18 of the 34 cases, the transverse diameter of the heart by Roentgen ray was less than 52% of the total transverse diameter of the chest, *i. e.*, well within normal limits. In 3 of the remaining 16 cases, it was over 57% of the total transverse chest diameter. In 10 of the 34 cases, there were inverted coronary-type *T* waves in Lead 1, 2, or both, while in 4 more of the 34 cases there were erect but low *T* waves in Lead 1 or 2. In the remaining 20 cases, the electrocardiograms were normal except that slight left axis deviation was present in a few. In only 2 of the 34 cases, did the ocular fundi show edema of the disks, and in 2 other cases there were small fresh hemorrhages. In all of the remaining cases there were varying degrees of arteriolar narrowing and arteriovenous nicking. In every case the renal function was good. In 26 of the 34 cases, the specific gravity of the urine was 1.024 or higher by a modified Mosenthal test, while in 13 of the 34 cases it was 1.028 or more. In no case was the specific gravity below 1.020. In 6 of the 34 cases, small amounts of albumin were noted inconstantly. Only 1 of the 34 cases was free of symptoms, while all of the others had headaches, dizziness, and other non-specific complaints.

In 16 of the 34 patients, blood pressure readings over 240 mm. systolic were occasionally found; in 13 of the 34 patients, readings over 250 mm. were occasionally noted. In 23 of the 34 patients, occasional diastolic readings in the clinic of over 130 mm. were found, and in 15 of the 34 patients, occasional diastolic readings of over 140 mm.

Methods. Each patient was given a mercury blood pressure manometer and a stethoscope. Either the patient or some member of the household was taught how to measure the blood pressure; those patients who determined their own blood pressure were given a special zipper cuff instead of the ordinary wrap-around cuff. The zipper cuff could be put on easily by the patient himself, thus dispensing with the need of another person for putting on the ordinary cuff. Patients were taught to regard as the systolic blood pressure the level at which the first appearance of a clear sound was noted. In the case of the diastolic reading patients were instructed to take the level of the complete disappearance of all sound as the diastolic blood pressure; this is sufficiently accurate for the purposes of this study and is easier to recognize than the more correct fourth phase. The patients were taught that the arm and blood pressure machine were to be kept on the horizontal level, the readings were to be taken in a quiet room without audience, the mercury was to be allowed to drop very slowly, and so on.[1] During the period of teaching, the determination of blood pressure was effected by means of a double stethoscope, so that at all times the authors heard exactly the same sounds as the patient or member of the household. All patients learned the procedure easily and thoroughly. In 13 of the 34 cases, the patients took their own readings, while in the remaining 21, some member of the household was taught to take them. The patient was instructed to make the readings twice daily; in the morning and in the evening. At each session, 4 readings were taken with intervals of at least 1 minute between readings. The average duration of each session for all patients was 12 minutes. Each patient was given special sheets of paper on which to record the readings, and was instructed also to record at each session any special symptoms or events. The patients were seen in the clinic or office at an average of once in 2 weeks. At such visits to the clinic, the patient was seated in a quiet room and the blood pressures were taken by the doctor during a 20-minute rest period, as described in previous studies.[2a] After this 20-minute rest period in the clinic the patient's ability to determine his blood pressure was frequently checked with the double stethoscope. This study differs therefore from that reported by Brown,[3] in 1930, of a patient with essential hypertension who took his own systolic blood pressure for 3 years. No correlation was made between clinic and home readings.

Results. More than 2800 clinic readings and 40,000 home readings were made in this study. The results will not be analyzed statistically; only obvious trends will be noted.

The average high readings (Column A, Tables 1 and 2) were usually the initial ones taken both at home and in the clinic. In 4 of the 34 cases, these average highest systolic readings were 50 mm. or more lower in the home than in the clinic; in 10 of the 34 cases, they were 40 mm. or more lower in the home, and in 15 of the 34 cases, they were 25 mm. or more lower in the home. In 8 of the 34 cases, the average highest diastolic levels in the home were 20 mm. or more lower than in the clinic, and in 12 of the 34 cases, were 15 mm. or more lower.

As a rule, the average lowest readings found (Column B, Tables 1 and 2) were those taken at the end of a 20-minute rest period in the clinic or taken last at each home session. In 4 of the 34 cases, the average lowest systolic readings were 30 mm. or more lower in the home than in the clinic; in 12 of the 34 cases, they were 20 mm. or

more lower in the home than in the clinic. These average maximal or minimal levels are not the occasional very high or low readings, but are actual average figures.

TABLE 1.—DIFFERENCES BETWEEN HOME AND CLINIC LEVELS OF SYSTOLIC AND DIASTOLIC BLOOD PRESSURE IN 34 CASES OF ESSENTIAL HYPERTENSION.

	A. Average highest clinic levels minus average highest home levels.	B. Average lowest clinic levels minus average lowest home levels.	C. Average clinic levels minus average home levels.	D. Average clinic levels during home study minus average home levels.	E. No. of weeks of home readings.
1	70/36†	30/14	50/25	40/16	H 13*
3	50/30	24/46	37/38	37/30	H 27
28	78/18	78/20	78/19	78/16	H 13
9	44/24	26/26	35/25	30/20	H 78
27	48/20	20/20	34/20	30/19	H 4
11P	50/20	18/20	34/20	30/18	P 30*
11H	30/0	8/6	19/3	7/−5‡	H 30
23	40/12	24/4	32/8	36/19	P 13
7	40/24	20/20	30/22	47/30	P 13
5	40/−4	16/26	28/11	35/13	H 10
21	40/8	32/10	31/9	20/7	H 17
4	36/10	−2/14	17/12	20/17	P 11
16	32/24	50/22	41/23	24/21	P 13
20	30/16	24/20	27/18	32/14	H 6
6	30/22	20/22	25/22	20/15	H 20
18	24/16	18/12	21/14	31/10	H 21
30	26/0	4/4	15/2	7/6	P 6
17	22/2	26/8	24/5	13/3	P 21
24	20/12	16/8	18/10	18/10	H 13
26	20/6	10/12	15/9	21/10	H 17
2	...§	...	...	22/15	P 4
13	...	...	...	25/12 = 1938 4/5 = 1939	H 94
34	24/14	12/10	18/12	−4/0	H 8
32	6/6	18/16	12/8	28/20	H 14
12H	14/10	0/10	7/10	12/15	H 94
12P	−20/46	−20/−4	−20/−10	5/5	P 94
14	12/16	2/6	5/11	3/3	H 4
19	10/10	0/10	5/10	4/5	P 9
8	10/2	10/4	10/3	7/−3	H 20
10	0/−24	16/4	8/−10	−1/8	H 7
22	...	...	...	5/6	P 12
15	...	...	...	7/2	P 52
29	0/−4	6/0	−3/−2	11/8	H 26
31	10/0	−10/0	0/0	−2/6	P 14
33	2/−4	4/4	3/0	0/5	H 10
25	10/2	12/8	11/5	10/5	H 15

* H = Blood pressure determination by member of household; P = when taken by patient.
† = 70 systolic/36 diastolic.
‡ "−" Indicates clinic reading lower than home reading.
§ Indicates no clinic readings before home study.

The chart of a patient with all her clinic and home readings accurately plotted is presented in Figure 1. The data in all cases were plotted in this manner. Figure 1 (Case 1) presents the blood

pressure readings of a female, age 47, with essential hypertension of 8 years' duration. Her 7-foot heart plate, electrocardiogram, and renal function were normal. Her ocular fundi showed moderate

TABLE 2.—SUMMARY OF TABLE 1.

(Number of mm. of Hg by which clinic readings excelled home readings in 34 cases of essential hypertension.)

No. of cases in each column of Table 1.		Systolic, mm. Hg.								Diastolic, mm. Hg.			
		50+.	40+.	35+.	30+.	25+.	20+.	15+.	10+.	30+.	20+.	15+.	10+.
	A	4	10	11	15	16	21	21	26	2	8	12	18
	B	2	2	2	4	6	12	18	21	1	10	11	19
	C	2	3	5	10	13	15	21	23	1	8	10	18
	D	1	3	6	11	13	19	20	23	2	5	14	20

narrowing of arterioles and moderate arteriovenous nicking. Figure 1 is divided into 3 parts: Part 1 presents clinic readings before the start of the home study; Part 2 the home readings together with the clinic readings during this period; and Part 3 the clinic readings during the 2 years following the cessation of home study. That portion of the chart above the 130 mm. level presents the systolic variations. The systolic blood pressure in the clinic during the years 1936 to 1938 varied from 164 to 240 mm. and this range is shown between the heavy horizontal black bands. However, in Part 2, the home readings, the home systolic range was 134 to 170 mm. In Part 3, the clinic readings from 1938 through 1940, the systolic variations are between 168 and 240 mm. The maximal levels of systolic blood pressure at home were 70 mm. of mercury less than in the clinic, while the lowest resting levels of systolic blood pressure at home were 30 mm. less than the lowest levels of the clinic readings both before and after the home studies. Similar, though less marked variations occurred in the level of diastolic blood pressure. The average home readings were roughly 50 mm. systolic and 25 mm. diastolic less than the average clinic readings before or after the home study. The clinic readings during the home study were somewhat less than the clinic readings before or after the home study, but still were much higher than the home readings. During the first 2½ weeks of the home study, the home readings were higher than subsequently. In the upper part of Figure 1, Part 2, are noted the times of the catamenia and the occurrences of headaches. On 3 of the 4 occasions when headaches were present there was an associated rise in the systolic blood pressure. These occurred when the patient was having her catamenia. The highest evening home

readings in Figure 1, Part 2, are shown by the round black dots and are almost invariably the peak readings of each day.

Discussion. In every one of the 34 cases of essential hypertension, the blood pressure readings taken at home by the patient or some member of the household were lower than those taken in the clinic by the doctor. These differences between home and clinic readings varied markedly in each case, depending on whether the readings were made before, during, or after resting. The maximum differences between home and clinic are found when the readings are made before resting. Since the common method of taking blood pressure

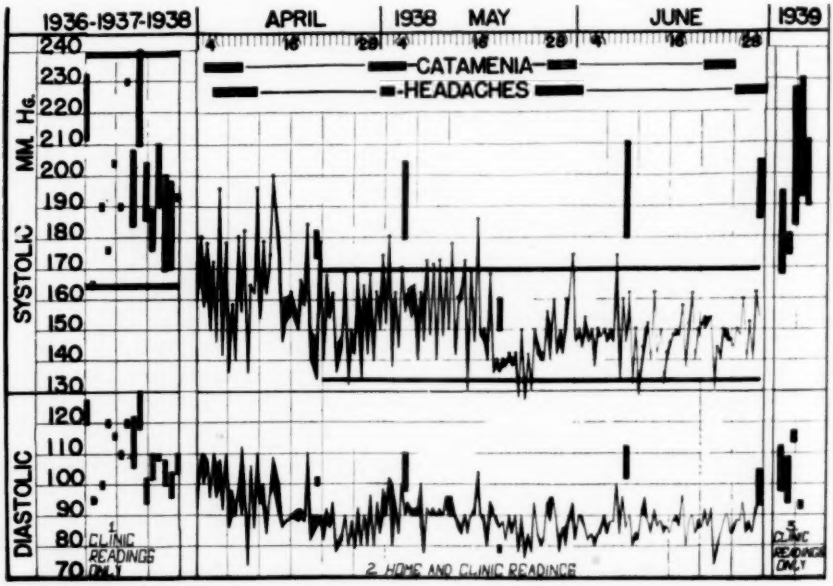

FIG. 1.—Comparison of clinic and home blood pressure readings in a patient with essential hypertension. Vertical broad black columns are clinic readings during a 20-minute rest period. Wavy lines in Part 2 are the home blood pressure readings taken by patient's daughter.

readings is to record the initial reading without rest, figures of differences between initial clinic and initial home readings here presented (Tables 1 and 2, Column A) may be applied to the experience of the general practitioner. Under such conditions, the home blood pressure level may be as much as 70 mm. of mercury systolic and 36 mm. of mercury diastolic lower than the clinic or office level (Case 1). Such great differences, as is true of all the figures in Tables 1 and 2, do not indicate occasional differences, but general ranges of blood pressure over an average period per patient of 104 weeks of special clinic study, and 23 weeks of subsequent home blood pressure study. Although the diastolic blood pressure did not vary as much as the

systolic, in 23% of the cases there was 20 mm. or more difference between the home and clinic diastolic readings. The great difference between the initial readings at home and in the clinic appears to be due to the excitement and tension associated with the visit to the clinic or doctor's office. This tension is present especially in hypertensive patients who possess a tense psychomotor makeup.[2d] In his home the hypertensive patient is presumably more relaxed and, therefore, his initial blood pressure reading under such circumstances is lower.

It appears reasonable that since excitement is more intense in the clinic than in the home, the clinic readings should drop the most on rest and approach closer to the home readings. The latter being taken with the patient already relaxed cannot drop very much further on rest and, therefore, home and clinic readings in this group are closer. On comparing the home reading after the patient had rested in a chair for 10 minutes or so, with the clinic reading after the patient had rested in the clinic for 20 minutes (Tables 1 and 2, Column B), the differences were, therefore, not as great as the differences between the initial readings.

In order to evaluate the possibility that during the period that the patient is taking his own blood pressure he may become calmer in the clinic in the presence of the blood pressure machine and doctor, an analysis was made of clinic readings during the period of home study. Column D, when compared with Column C shows that the average level of these readings in the clinic during home study are close to the average levels in the clinic before the home study.

It was found that the difference between home and clinic readings was in general the same in those patients who took their own readings and those who had some member of the household take the blood pressure. However, in 2 individual instances, a change from having a member of the household take it to having the patient himself take it, resulted in somewhat different levels of blood pressure being found. In 1 (Case 11) the levels became lower when the patient took his own blood pressure and in the second (Case 12) higher. The effect of different individuals on 1 patient was well illustrated in Case 25 where first one daughter, a high-strung, talkative individual, took the blood pressure. When a calmer more relaxed daughter later took over the duties of making the readings, the readings were lower. This effect of the doctor or nurse on the patient is often seen in practice where an excitable brusque doctor will cause much higher readings than a calm physician.

In the one case when a patient took his own readings and obtained higher readings than when a member of the household took them, this was due probably to the failure to relax properly. This does not indicate that he had developed a neurosis and was thereby being harmed. Indeed in no case has a neurosis developed as a result

of this study. In 1 case, however, the patient became upset when she found that her blood pressure at home was normal in the morning and high in the evening, and that she could not cause the evening readings to remain normal; in this case it was decided to stop her home study.

There were 11 cases that even in their initial systolic readings had only slight differences between home and clinic—less than 20 mm. systolic difference. These cases are the 11 cases at the bottom of Table 1. In most of these cases, the fluctuations of blood pressure during the rest period or from day to day were comparatively small. In this group of 11 cases, 2 (Cases 14 and 8) have already died of cerebral hemorrhage, while there have been no deaths in the remaining 23 patients during the 1½ years that have elapsed since these deaths. The 2 former patients had choked disks. One severe case (Case 10) has been helped by at least a temporarily successful sympathetic nerve resection operation. The reason for so little fluctuation in these cases is hard to understand. Four of these cases were males, while only 5 of the remaining 23 cases were males; the significance of this finding is not clear. It is to be noted, however, that in general essential hypertension seems to be more severe in the male.

VALUE OF METHOD. 1. *Teaching the Patient Knowledge of His Chronic Disease.* After weeks or months of taking their own blood pressure twice a day patients begin to understand fully some of the characteristics of their disease. They become aware that their blood pressure rises when they are under strain, worry, hard work, or hard play. One patient noted regularly that when he played cards in the evening his blood pressure was high when he arrived home despite the fact that he had not noticed himself excited during the game. Others noted the relationship of a cold house to high readings. It also has taught them how quickly high readings will drop on relaxation in a chair. They have noted the relationship of headaches and other symptoms to their blood pressure level. In general, it has seemed to make them less fearful of the disease and more prudent in their activities.

2. *Teaching the Physician.* The method also instructs the physician concerning the above points, and also gives him the opportunity to observe the natural course of the disease. It may make easier the search for the factors that adversely affect the disease.

3. *Prognosis of the Disease.* The method may possibly help in evaluating prognosis. For example, Cases 14 and 8 both had choked disks as evidence of severe disease, and both also had only slight variation between home and clinic; death occurred early in these patients. On the other hand, we feel that this method may have value in deciding the prognosis to be much better in those who have definitely lower readings at home than in the office or clinic. These much lower readings at home which we have presented in Figure 1

and Table 1 must help many physicians understand why some of their supposedly severe hypertensive patients have lived many years. The common statement that a given patient has lived 20 years with a blood pressure of 250 mm. may mean that the patient has spent most of these 20 years with a blood pressure of perhaps 170 or 180 mm., except when she sees her physician or has a momentary period of other excitement. Further data on prognosis are now being gathered.

4. *Evaluation of Therapy.* Probably the greatest value of the home blood pressure method is the evaluation of treatment. In our own attempts to evaluate treatment we have in the past[25] advocated a rather elaborate method of control blood pressure readings. The home blood pressure method has given so much clearer, clean-cut results in determining the effects of treatment that this method should be considered for all clinical research in blood pressure. Data already obtained on the effects of various drugs in hypertension (which will be published separately) strongly suggest that all forms of therapy for hypertension should be restudied by this method.

It must be emphasized that these results are presented not for the purpose of having the 1,000,000 or more hypertensives in the United States secure blood pressure machines or of having the method adopted for general office use. The home blood pressure method should for the present be reserved for the occasional case in practice and for most instances of research in the treatment of essential hypertension.

Summary and Conclusions. Thirty-four patients with various degrees of essential hypertension had their blood pressure studied over a long period in the clinic and at home. The home readings have been very carefully taken twice daily for weeks or months by the patient or a member of the household. This study shows that the home systolic and diastolic blood pressure readings are lower than the clinic readings in all cases of essential hypertension. In 30% of the cases the systolic home blood pressure readings were 40 mm. or more lower than in the clinic, and in 24% the diastolic home readings were 20 mm. or more lower than the clinic readings. The method caused no neurosis or harm in any patient. Those patients with only slight difference between home and clinic readings had in general comparatively little fluctuation of blood pressure from day to day. The home blood pressure method should be of value to teach the patient the nature of his disease, to help the physician observe better the natural course of the disease, to aid in the prognosis of the individual case, and to permit the clear-cut evaluation of therapy.

We wish to thank the Baumanometer Company for the loan of mercury blood pressure machines, and G. P. Pilling & Sons for the loan of stethoscopes. Zipper cuffs are made by the Boulitte Company.

REFERENCES.

(1.) Am. Heart Assn. and Cardiac Soc. of Great Britain and Ireland, Am. Heart J., **18**, 95, 1939. (2.) **Ayman, D.**: Normal Blood Pressure in Essential Hypertension, (*a*) J. Am. Med. Assn., **94**, 1214, 1930; (*b*) Ibid., **95**, 246, 1930; (*c*) Ibid., **96**, 2091, 1931; (*d*) Am. J. Med. Sci., **186**, 213, 1933. (3.) **Brown, G. E.**: Daily and Monthly Rhythm in the Blood Pressure of a Man with Hypertension, Ann. Int. Med., **3**, 1177, 1930.

DELAYED ELECTROCARDIOGRAPHIC CHANGES IN CORONARY OCCLUSION.*

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The importance of electrocardiographic changes in coronary occlusion have been frequently stressed. Wilson[3] has, however, expressed a desirable caution in regard to their diagnostic value: "In coronary occlusion the electrocardiogram is often so characteristic that it is possible to make a positive diagnosis without other data. In general, however, it is most unwise to base any diagnosis which involves a commitment as to the presence of a coronary abnormality of any kind upon the electrocardiogram alone." Later he says: "The electrocardiogram is most useful when it is interpreted by the physician in charge of the patient." These facts are borne out in the present study in which 5 instances are reported wherein the absence of significant electrocardiographic changes in the early stages of coronary occlusion might easily have been misleading. Attention has been called to such situations in the past. Thus, Feil[1] states: "A normal record including chest leads should not rule out a developing coronary thrombosis," and Sampson and Eliaser[2] reported cases in which the electrocardiogram offered them no assistance in making a diagnosis of impending thrombosis.

Case Reports. Case 1.—A. C. S., a male, aged 59, was first seen in my office August 19, 1929. He had had, 10 days previously, a sensation of pressure and heaviness over the sternum radiating down the left arm. At this time there were no findings other than a marked arcus senilis. An electrocardiogram was taken which appeared normal (Fig. 1*A*). He was confined to his rooms but not to bed. About 3 days later he complained of slight precordial pain. On this examination a pericardial rub and a systolic murmur at the tricuspid area were heard. The rub persisted until August 30. The temperature rose to 100.4° F. and was normal after August 30th. The leukocyte count on August 24 was 7200, with 79% neutrophils. The blood pressure was 126/84. The electrocardiogram taken on August 29, 1929 (Fig. 1*B*) showed relatively minor changes; on September 10, 1929, after the disappearance of the rub, T_1 and T_2 were rather sharply inverted (Fig. 1*C*). On January 31, 1930, the electrocardiogram had returned to normal (Fig. 1*E*).

* Aided by the A. D. Nast Fund for Cardiac Research and the A. B. Kuppenheimer Fund.

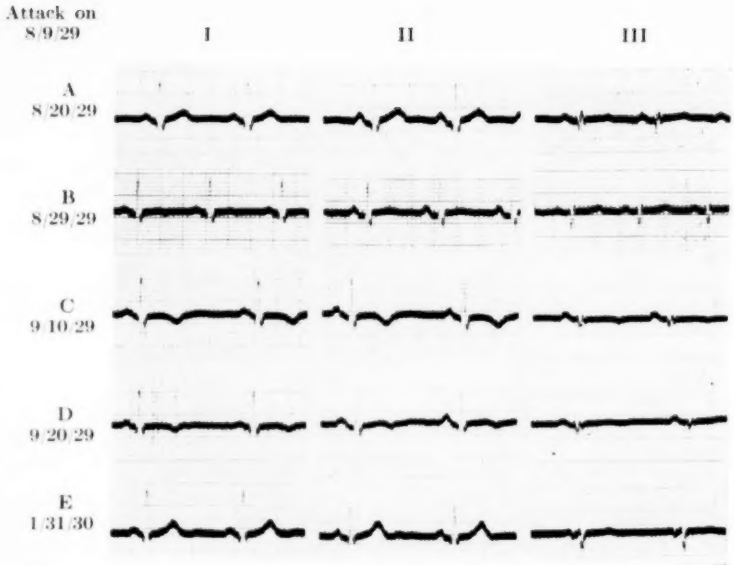

CHART 1.—Case 1. Record A was taken 11 days after the initial attack; B, 7 days after the disappearance of the rub; C, 11 days after the disappearance of the rub; D shows a slight regression and E, the return to normal.

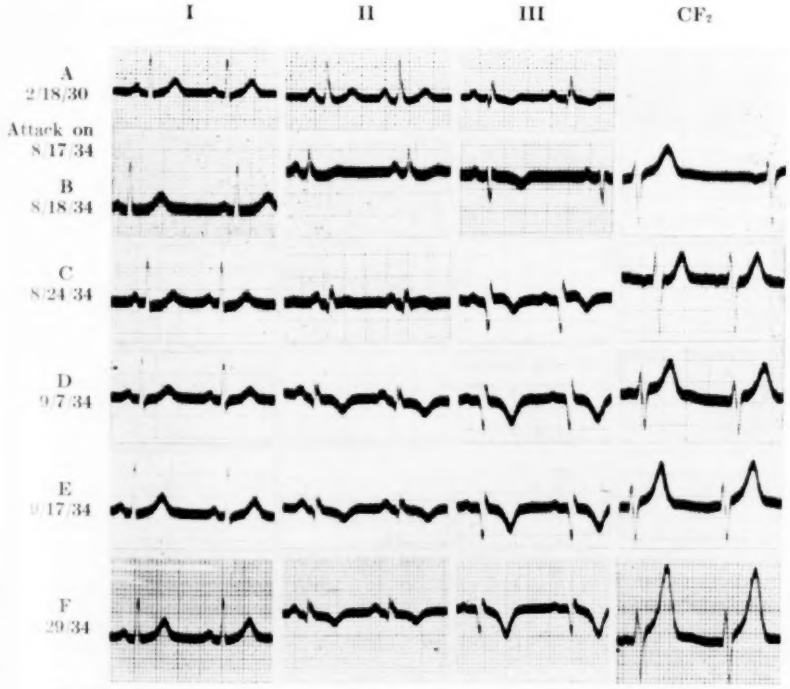

CHART 2.—Case 2. Record A was taken 4 years before the attack; B, 24 hours after the attack and C, D, E and F, respectively, 1, 3, 4, and 6 weeks after the attack.

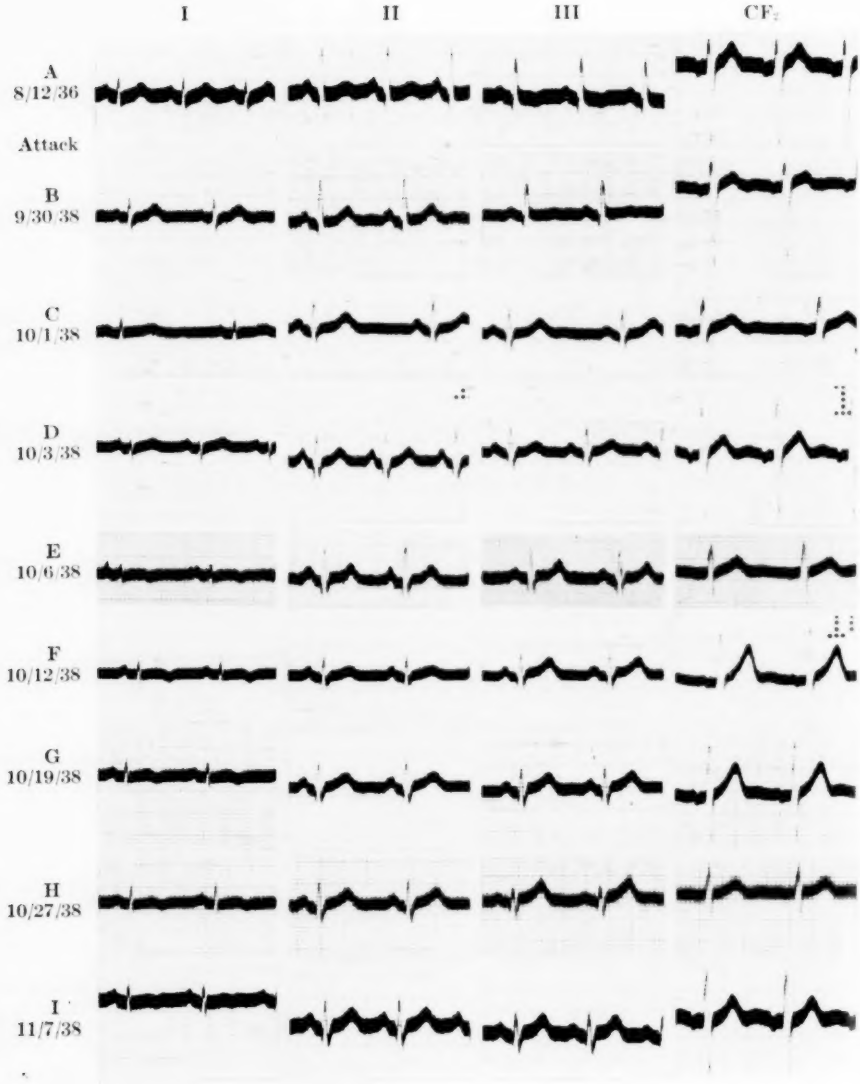

CHART 3.—Case 3. Record A was taken 2 years before the attack; B, on the day of attack and C, D, E and F, respectively, 1, 4, 7 and 13 days after the attack. G, H, I, respectively, 3, 4, and 5½ weeks after the attack.

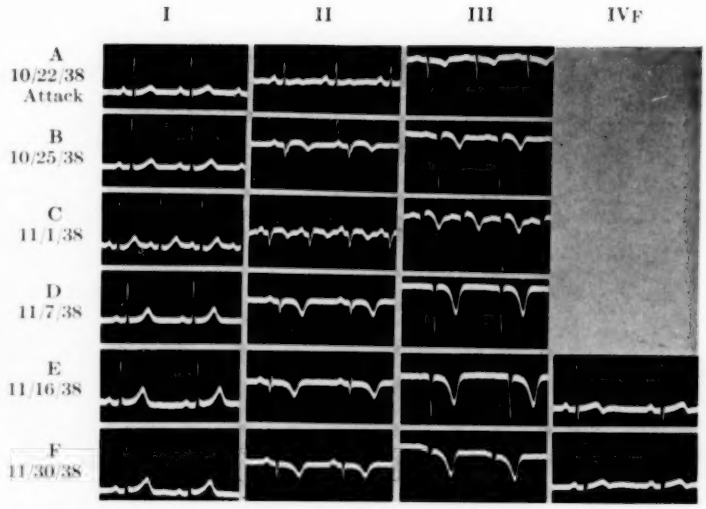

CHART 4.—Case 4. Record A was taken on the day of the onset. B shows a typical record of a posterior wall type of infarction; C, further progression; D, regression with S–T_2 and S–T_3 now isoelectric; E, still further regression, and F a more stabilized record.

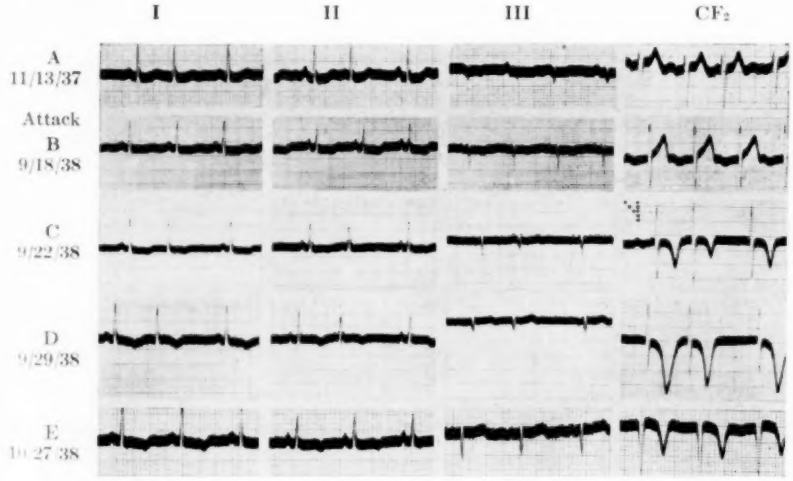

CHART 5.—Case 5. Record A was taken 10 months before the attack; B, on the day of the attack; C, 4 days after the attack and shows changes, especially in lead CF_2; D, 11 days after the attack and shows further changes in all leads. E shows regression.

Comment. In this case the diagnostic electrocardiographic changes first appeared 20 days after the initial attack and 7 days after the appearance of the pericardial rub. The most marked changes occurred 19 days after the onset and 11 days after the disappearance of the rub. These electrocardiographic changes might have been due in part to pericarditis although there were never any signs of a pericardial effusion. The only reasonable cause for the pericarditis in this case was a myocardial infarct.

CASE 2.—S. N., a male, aged 42, when first seen at the office on February 17, 1930, complained of vise-like pain in the right chest radiating to the back. He was seen at intervals and showed no change in his condition. He was a heavy smoker and drank 3 cups of coffee a day. There was no history of alcohol. His blood pressure on these visits was approximately 135/85. At 2 P. M. on August 17, 1934 he had a moderate precordial pain radiating through to the back while walking back to his office from lunch. This gradually became worse, reaching its height at 11 P. M. At this time it was a "tight-pressing and gripping sensation over the heart." He felt weak, perspired profusely and had considerable belching. He entered the Michael Reese Hospital at 12:50 P. M. on August 18, 1934, feeling improved. At this time he stated that he had been awakened 2 months before with a sharp burning pain in the right arm radiating to the precordium and down the arm to the little finger. This was accompanied by shortness of breath. Since, then, this pain had recurred frequently during the day. It came on with exertion, lasted ½ hour and left a feeling of soreness.

Examination on entrance showed very few abnormalities. The apex beat was neither visible nor palpable. The heart sounds were distant and muffled. The blood pressure was 108/74; on discharge it was 112/80 and ranged from 98/68 to 118/72. On admission the patient's temperature was 98.9° F., pulse rate 64 and leukocyte count, 11,300. From August 19 to August 22 his temperature ranged from 99.6° to 102° F. and his pulse from 62 to 84. The temperature was normal on August 26 and remained so until discharge on September 29, 1934.

Comment. The electrocardiogram taken 24 hours after the attack showed only minor changes which could have been due to a progressive coronary sclerosis over the 4-year period which elapsed between the electrocardiograms (Fig. 2*A* and *B*). This was interpreted as such by the electrocardiographer. Later electrocardiograms (Fig. 2*C*, *D*, *E* and *F*) showed a typical posterior wall infarction of the Q_3T_3 type, with healing. Symptoms and findings from the beginning were typical of a coronary occlusion.

CASE 3.—A. W., a male, aged 45, was first seen at the office in August, 1936, for pain in the right shoulder. His findings were negative at that time and subsequently except for a marked arcus senilis. His blood pressure ranged from 124/90 to 104/70. On September 30, 1938, he telephoned from the railroad station, saying that he had some precordial pain following exertion on the previous evening and again that morning on running for the train. These pains recurred in the office on excitement and in the hospital while taking off his shoes, being relieved each time by nitroglycerine. At 4 P. M. while in bed the pain recurred, was much more severe and lasted for over 12 hours even with morphine, and radiated to the neck and both arms. He now gave a history of having had slight precordial pain one month previously which he had ignored. With the pain at this time, there was some perspiration and pallor.

Examination showed a pulse rate of 65, no murmurs or rub and a somewhat accentuated A_2. Blood pressure at 4 P. M. was 160/110, at 9 P M. it was 140/85. On October 1 his blood pressure was 168/108. From that time on it fell and on discharge was 110/75. The leukocyte count on October 1 was 24,000 with 74% neutrophils; on November 8 it was 11,600, with 56% neutrophils. Temperature on entrance was 99.2° F. and ranged from 98.6 to 100.8° F. up to October 6 after which it was normal. On October 3, 1938 a scratchy sound was heard during systole along the left sternal margin in the fourth and fifth interspaces. The latter can still be heard at times but is much fainter. On October 1 there was 2+ sugar in the urine; this had been absent previous to this and since that time. The blood sugar was 99. Roentgen ray showed a normal heart contour with a cardio-thoracic ratio of 12/28.3.

Comment. The electrocardiogram taken on the day of the attack showed practically no changes from that taken 2 years before (Fig. 3*A* and *B*). In fact, there were very few changes throughout the entire course of electrocardiographic records. The only difference of note was that T_1 gradually became smaller until 2 weeks after the onset of the attack at which time it was definitely inverted (Fig. 3*F*) and this change persisted with a little waning; at the same time T_3 became positive. In this instance, we have a patient with comparatively minor electrocardiographic changes, definitely out of line with the history and findings of a coronary occlusion.

Case 4.—A. P., a short, obese male, aged 41, an elevator operator entered my service at the Cook County Hospital on October 22, 1938. For 2 weeks prior to entrance he had complained of fatigue and some dyspnea on exertion. On the morning of entrance while coming to work he was suddenly seized with a severe constricting substernal pain radiating to both shoulders and arms. He felt as if he would choke. He was admitted to the ward in shock, with cold, clammy skin. He was cyanotic. The pain was relieved by morphine, after several hours. Mild shock continued for several days. The findings were essentially negative. There was no fever. The blood pressure was 130/90 on entrance, 115/80 on October 24, and went as low as 90/50 on November 12. The leukocyte count was 8500 on October 23 and 15,000 on October 27.

Comment. The electrocardiogram taken on the day of onset of his attack (Fig. 4*A*) showed no changes other than those which could be accounted for by his stature, namely, a deeply inverted QRS_3, an inverted T_3. The diphasic T_2 was unusual. Four days later, however, the changes were characteristic of a posterior wall infarction (Fig. 4*B*). Subsequent records (Fig. 4*C*, *D*, *E*, *F*) confirm this impression and show finally some regression. No chest leads were taken for the first 25 days. After this time the changes in the chest leads were insignificant as compared to the limb leads and it might be assumed perhaps without justification that this would have held true for previous electrocardiograms as well.

This is an instance in which the diagnostic changes in the electrocardiogram occurred several days after a typical onset of coronary occlusion.

Case 5.—J. G., a female, aged 63 was seen by me in November, 1937. At this time she had a hemorrhage from the rectum which was and is of unknown etiology. She gave a history of having had high blood pressure

which at the time of this examination was 226/118. There were numerous extrasystoles of auricular origin giving a trigeminus. A_2 and P_2 were both accentuated. The heart was normal in size and shape as shown by percussion and fluoroscopy. The thoracic aorta was diffusely dilated. On September 18, 1938, she again entered the hospital. She had had an attack of epigastric pain on September 13, diagnosed as angina. This recurred on September 14, and was diagnosed as "gas" and had appeared intermittently since then, always relieved by nit oglycerine. On the morning of the 18th, these pains became severe and constant and radiated to the back and both arms and were *not* relieved by nitroglycerine but were partially relieved by morphine. She was brought to the hospital in an ambulance and upon entrance had a cold sweat, a week pulse and nausea. These lasted for only 2 minutes when the pulse became full and bounding with a rate of 96. The heart was of the same size as on the last admission. A_2 was loud and ringing. There was a systolic murmur over the pulmonic area and a fainter one over the aorta. Occasional extrasystoles were present. The next day the interne heard a friction rub. A pulsus bigeminus occurred which cleared up with atropine, gr. 1/200. This also relieved to some extent the nausea and the "indigestion" pains radiating to both arms. On November 20 she was sent home though she still had epigastric pain radiating to both arms. There was no fever at any time during the hospital stay and her blood pressure ranged from 108/70 on October 17 to 178/124 on September 21. The leukocyte count was normal. The blood pressure taken at her home on January 14, 1939, was again 230/120. She has continued to complain of epigastric pain radiating to both arms.

Comment. This patient at no time gave a clear clinical picture of coronary occlusion. Her symptoms and the electrocardiographic changes shown in the series of records in Figure 5 make it appear fairly certain that she had a coronary occlusion. However, the electrocardiographic changes did not appear until 4 days after the attack (Chart 5*C*). The changes between *A* and *B* could have been due to progressive coronary sclerosis. Furthermore, there were mild anginal attacks 4 days before the severer one without any changes in the electrocardiogram. This case is in accord with the findings of Feil[1] and Sampson and Eliaser.[2]

Summary. Five cases are reported in which the diagnosis of coronary occlusion was clear clinically from the start, the electrocardiograms showing changes only after a lag of several days. In 1 instance (Case 3) the changes were minimal and not definitely diagnostic without the patient's history.

Conclusions. 1. An adequate history is all-important in the diagnosis of coronary occlusion, as in all diseases.

2. The diagnosis cannot be left to the cardiographic laboratory alone but must be made by the clinician on the basis of all the available data.

3. Negative or inconclusive electrocardiographic findings do not exclude the presence of a coronary occlusion.

I wish to express my appreciation to Dr. L. N. Katz for his valuable suggestions in preparing this report and to Miss B. Phillips for her technical assistance.

REFERENCES.

(1.) **Feil, H. S.**: Am. J. Med. Sci., **193**, 44, 1937. (2.) **Sampson, J. J.**, and **Eliaser, M.**: Am. Heart J., **13**, 683, 1937. (3.) **Wilson, F. N.**: *In* Diseases of the Coronary Arteries and Cardiac Pain, edited by Robert L. Levy, New York, The Macmillan Company, p. 326, 1936.

CARDIAC AND RESPIRATORY FUNCTION AT REST IN PATIENTS WITH UNCOMPLICATED POLYCYTHEMIA VERA.

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POLYCYTHEMIA vera is associated with a marked increase in the volume and viscosity of the blood, changes which should influence hemodynamics to a considerable degree. All observers are in agreement that slowing of the peripheral blood flow occurs;[10a,b,11,45] the clinical manifestations of the disease are regarded as secondary to retardation of the rate of blood flow.[21] The possible effects of the hematologic changes of polycythemia vera on cardiac function have been discussed by a number of authors with divergent conclusions. Thus Goldsmith[18] states that the cardiac output is abnormally high, due probably to the very large blood volume, and Burton-Opitz[12] concludes that the cardiac work is increased as a result of increased viscosity of the blood. Other authors, however, have recorded data indicating that both are normal. It was therefore considered desirable to study the cardiovascular dynamics of polycythemia vera before and after treatment; because of the close relationship between cardiac and pulmonary function, studies of the respiration have also been made. A large number of publications bearing on this problem are available; since there is no adequate review of this literature in the English language, discussion of the cardiovascular dynamics of polycythemia vera will include reference to these reported data as well as to the findings of the present study.

Materials and Methods. Three patients, ranging in age from 38 to 48 years were studied; 2 were males. Only relatively young patients without hypertension were selected for study in order to isolate to as great a degree as possible the effects of the polycythemia itself. In 2 patients (Cases 2 and 3) studies were made before treatment had been instituted and again after the red blood cell count and hemoglobin had been brought to approximately normal levels by means of repeated venesection.

All measurements of cardiovascular or respiratory function were made with the patient in the post-absorptive state under basal conditions in the semi-recumbent position after a rest of from ½ to 1 hour. The cardiac output was measured by the ethyl iodide method of Starr and Gamble,[42] the pulse rate, basal metabolic rate, respiratory quotient, alveolar air carbon dioxide content and respiratory rate and minute volume being determined at the

same time. The values reported represent the average of the results of several determinations. The arteriovenous oxygen difference was calculated from the oxygen consumption and the cardiac output. Following the determination of the cardiac output the arterial blood pressure was measured. The figures in the tables represent the averages of several readings. The venous pressure was then determined by the direct method of Moritz and von Tabora.[38] Following this the velocity of blood flow was estimated, using as an index the "arm-to-tongue" circulation time as measured with decholin.[16] Finally the vital capacity was measured.

The following methods were employed in the hematologic studies: for hemoglobin, that of Haessler and Newcomer;[20] for blood volume, that of Keith, Rowntree and Geraghty;[28] for viscosity, that of Hess;[23] for hematocrit, that of Wintrobe.[44] The values reported are the averages of 2 or more measurements. Most of the hematologic studies were made on the same day as the cardiovascular and respiratory measurements; a few were made several days earlier or later.

Observations. All 3 patients studied before treatment showed striking increases above normal in red blood cell count, hematocrit, and blood volume and viscosity; the cardiovascular and respiratory functions measured at this time were, however, within normal limits (Table 1), with the exception of a slight elevation in basal pulse rate. No striking changes in cardiovascular and respiratory dynamics, except for some slowing of the basal pulse rate and in 1 case some acceleration of the arm-to-tongue circulation time occurred as a result of changes in the blood to or toward normal (Table 1) in the 2 patients studied after treatment.

TABLE 1.—DATA ON 3 CASES OF POLYCYTHEMIA VERA.

	Case 1.	Case 2.		Case 3.	
	Before treatment.	Before treatment.	After treatment.*	Before treatment.	After treatment.†
Sex	F	M		M	
Age, yrs.	38	44		39	
Blood volume, cc per kg.	136	132	81	137	
Red blood cell count per c.mm.	8,370,000	9,900,000	6,900,000	7,940,000	5,810,000
Hemoglobin, gm. per 100 cc.	17.8	23.8	13.8	24.2	15.2
Hematocrit, % cells	66	76	49	72	53
Mean cell volume, c.mm.	79	77	71	91	91
Viscosity	10.0	15.3	6.7	10.0	6.1
Alveolar air CO_2, %	4.8	5.2	5.6	5.8	5.8
Basal metabolic rate, %	+3	+16	+12	−15	−8
Respiratory quotient	0.81	0.80	0.83	0.83	0.85
Respiratory rate per minute	12	18	15	18	14
Respiratory minute volume, liters per sq. meter per minute	3.0	4.0	3.5	3.4	3.3
Vital capacity, liters per sq. meter per minute	1.5	2.4	1.8	1.7	2.1
Cardiac minute volume output, liters per sq. meter per minute	2.3	2.1	2.1	2.2	2.2
Arterio-venous O_2 difference, vol. %	5.61	7.41	7.36	5.16	5.60
Pulse, beats per minute	89	78	66	79	60
Circulation time, seconds	13	18	15	14	15
Venous pressure, cm. H_2O	3.1	9.6	6.5	9.3	9.8
Arterial pressure, mm. Hg	120/70	135/80	135/80	120/80	110/80

* Ten weeks later.
† 17 weeks later.

Discussion. 1. *Cardiac Output.* The cardiac output at rest has been reported within normal limits by a number of workers using older, inaccurate methods[6,30,36,40] as well as by authors using methods acceptable today;[14,17,29] a total of approximately a dozen patients

have been studied. Goldsmith's[18] findings of a markedly increased cardiac output in 2 of the 4 patients studied by her is difficult to explain, although it is to be noted that in the one patient most thoroughly studied a close correlation between cardiac output and basal metabolic rate existed, so that the increase in minute volume output of the heart must have been related to the increased metabolism. Brooks[9] obtained normal values for cardiac output in 1 of 2 patients studied. The other, who showed a considerable increase in cardiac output was clearly one of secondary polycythemia with marked pulmonary disease, clubbing of the fingers, incapacitating dyspnea, carbon dioxide retention and a striking decrease in arterial blood oxygen saturation; the validity of estimations of cardiac output by a foreign gas method in patients with severe pulmonary disease is questionable.

The results of the present study are in agreement with those of the majority of workers in this field: the cardiac output at rest in polycythemia vera is normal.

2. *Cardiac Work.* The work of the left ventricle is readily calculated from the formula of Evans and Matsuoka[15] as follows:

$$W = O\,P + \frac{w\,V^2}{2g}$$

where W = work, O = output, P = arterial resistance (mean blood pressure $\times$ 13.6), w = weight of the blood, V = velocity of blood in the aorta, and g is the gravitational constant. In ordinary usage the factor $\frac{wV^2}{2g}$ is disregarded since it usually comprises no more than 1 to 3% of the total work of the left ventricle.

Since the cardiac output and the blood pressure are normal in uncomplicated polycythemia vera, it is clear that the work of the heart, at least in the resting subject, is normal.

3. *Pulmonary Circulation Time.* The pulmonary circulation time parallels the cardiac output but is also an indication of the degree of pulmonary engorgement.[2,3] The arm-to-tongue time may be normal[17,25] or slowed.[4,8,25,43] Tarr[43] *et al.* found values of 18 seconds in 2 cases and considered them prolonged; these values are probably within normal limits. Similarly the ether time may be either normal[4,25] or prolonged.[25] In the present study normal values were found in all 3 patients, although a significant acceleration occurred after treatment in 1 case.

4. *Venous Pressure.* The venous pressure was normal in all studies in the present investigation, agreeing with the findings of previous workers.[17,25]

5. *Lung Volume and its Subdivisions.* The respiratory rate and minute volume may be increased in patients with polycythemia vera, especially in those with elevation of the basal metabolic rate. The residual air is normal or slightly increased[9,22] as is the midcapacity.[22] Considerable difference in values for vital capacity have been recorded by various workers: Isaacs[27] and Brooks[9] found it low,

Blumgart *et al.*[8] found it low in 1 case with heart disease and normal in an uncomplicated case, while other authors[22] have reported normal values. In the present study normal values were found in 2 cases and a slight diminution in 1. No change was effected in the 2 treated cases by therapy. Brooks[9] reported a similar finding in a patient with diminished vital capacity. It seems unlikely, therefore, that the low vital capacity found in some patients with polycythemia vera is due directly to the increased blood volume and viscosity.

Since the vital capacity is an important part of the total lung volume, reported values for the latter can be expected to differ according to whether the former is normal or low. Thus Harrop *et al*[22] reported normal values for total capacity, while Brooks[9] found it diminished in his 1 case of polycythemia vera.

6. *Blood Oxygen Content and Saturation.* An important indication of the functional capacity of the lungs is the oxygen saturation of the arterial blood. All authors[6,9,22,24,36,40] report normal values; the capacity is greatly increased but the content increases in proportion. The finding of Harrop *et al*[22] that the arterial oxygen saturation decreases after exercise is difficult to explain unless exercise induces in polycythemic patients extremely rapid shallow breathing.[34] The venous blood oxygen saturation is within normal limits;[27,32,37] here again the capacity is elevated and the content is also increased. Since the arterial and venous blood oxygen contents are increased to the same degree, the arterio-venous oxygen difference must be normal.

7. *Blood Carbon Dioxide Content and Combining Power.* The carbon dioxide combining power in polycythemia vera is rather low[27] as is the carbon dioxide content of the venous blood.[32,37] This is due at least in part to the fact that the blood cells contain only about 60% as much available base as serum. Since a given unit of polycythemic blood contains as much as 70 to 80% cells, as compared to the normal value of 45%, it is clear that lowering of the whole blood carbon dioxide content and combining power must occur although there is no detectable abnormality in the electrolyte pattern of the serum.

Another factor contributing to a lowered blood carbon dioxide content may be hyperventilation due to stimulation of the respiratory center by factors other than carbon dioxide retention; this will be discussed elsewhere.

8. *Basal Metabolic Rate.* The metabolic rate may be high,[1,7,9,17,18,21,26,27,31,33,35,40,41] normal,[5,6,7,14,18,19,21,33,40] or occasionally low[29] in patients with the disease. In the present study the metabolism was essentially normal in all instances and was not influenced by therapy. Bliss[7] treated 10 patients and found no consistent change in basal metabolic rate. Goldsmith's[18] patient with an elevated basal metabolic rate showed some decrease after treatment while Brooks'[9] showed no change. The cause of the increase in metabolic rate in polycythemia vera is not definitely known but it may be the

increased respiratory activity of some patients. Resnik and Friedman[39] have shown that increased respiratory activity in patients with congestive failure is associated with elevation of the basal metabolic rate; a similar situation may exist in polycythemia vera.

9. *Capillary Blood Flow.* The velocity of capillary blood flow as visualized in the nail beds is greatly diminished.[10a,b,11,45] The capillaries are elongated, tortuous, and, especially in the venous segments, greatly distended. The small venules are also engorged. The blood cells move through the capillaries in broad columns instead of single file.

A similar phenomenon is observed in congestive failure,[2] but is associated with a diminished cardiac output. In polycythemia vera, however, the output of the heart is normal and the slow flow observed must therefore be due to peripheral factors. The marked vasodilation which is due to increased blood volume can account for some of the slowing. Nevertheless, a normal amount of blood enters each part of the body via the arteries and leaves via the veins, as evidenced by the normal values found for cardiac output and arteriovenous oxygen difference. An explanation for the occurrence of this phenomenon in spite of marked slowing of blood flow is the considerable increase in blood volume observed in polycythemia vera. The slowing of blood flow due simply to capillary dilation is not physiologically important in this disease since its effects are counteracted by increased blood volume. Indeed, it is possible that the vasodilation is merely secondary to the increased blood volume.

There is no mechanism completely balancing the action of increased blood viscosity in slowing the capillary blood flow. Poiseuille's law states that if the force remains the same, the velocity of a moving liquid in a capillary varies inversely as the viscosity. Other factors also influence the velocity, as can be seen from the formula.

$$v = \frac{\pi r^4 P}{8\eta l}$$

where v = velocity, r = radius of the capillary, l = length of the capillary, η = viscosity of the liquid and P = propelling pressure. Thus dilatation of the capillaries counteracts to some extent the effect of viscosity and lengthening the capillary exaggerates it. It is to be noted however[10a,b,11,45] that there is little or no dilatation of the arterial loop of the skin capillaries in polycythemia vera, so that the marked dilatation of the venous limbs of the capillaries does not serve to counteract the slowing effect of the blood viscosity as much as it might.

The applicability of Poiseuille's law, based on studies on systems of rigid tubes, to conditions within the animal body has been questioned but the experiments of du Bois-Reymond[13] on isolated animal organs clearly demonstrate the validity of Poiseuille's conclusions when applied to the elastic vessels of the animal body.

The only striking abnormal cardiovascular finding resulting from available studies on polycythemia vera is marked slowing of periph-

eral blood flow. The data obtained in the present study, together with the findings of other authors here reviewed, indicate that cardiac output and work are normal in patients with polycythemia vera, at least at rest. It must be concluded, therefore, that the increased volume and viscosity of the blood impose no abnormal burden on the heart. A corollary to this conclusion is that the slow peripheral blood flow of polycythemia vera is due solely to peripheral factors. Studies of the physiology of the peripheral vascular system in this disease will be the subject of another communication.

Summary and Conclusions. 1. Measurements of cardiac and respiratory function in patients with polycythemia vera at rest are normal.

2. The slowing of blood flow, and the symptoms associated with it, are not due to impaired cardiac function but rather to increased resistance to the flow of blood through the small capillaries. This is due largely to increased viscosity of the blood.

The patients used in this study were very kindly referred to us by Dr. William Dameshek.

REFERENCES.

(1.) **Abbott, M. E.**: Canad. Med. Assn. J., **8**, 491, 1918. (2.) **Altschule, M. D.**: Medicine, **17**, 75, 1938. (3.) **Altschule, M. D.**, and **Gilligan, D. R.**: J. Clin. Invest., **17**, 401, 1938. (4.) **Baer, S.**, and **Slipakoff, B.**: Am. Heart J., **16**, 29, 1938. (5.) **Barer, A.**, **Paul, W. D.**, and **Baldridge, C. W.**: J. Clin. Invest., **13**, 15, 1934. (6.) **v. Bergmann, G.**, and **Plesch, J.**: München. med. Wchnschr., **58**, 1849, 1911. (7.) **Bliss, T. L.**: Ann. Int. Med., **2**, 1155, 1929. (8.) **Blumgart, H. L.**, **Gargill, S. L.**, and **Gilligan, D. R.**: J. Clin. Invest., **9**, 679, 1931. (9.) **Brooks, W. D. W.**: Proc. Roy. Soc. Med., **29**, 1379, 1936. (10.) **Brown, G. E.**, and **Giffin, H. Z.**: (*a*) Am. J. Med. Sci., **166**, 489, 1923; (*b*) Ibid., **171**, 157, 1926. (11.) **Brown, G. E.**, and **Sheard, C.**: J. Clin. Invest., **2**, 423, 1926. (12.) **Burton-Opitz, R.**: J. Am. Med. Assn., **57**, 353, 1911. (13.) **du Bois-Reymond, R.**, **Brodie, T. G.**, and **Müller, F.**: Arch. f. Physiol., Suppl., p. 37, 1907. (14.) **Ernst, C.**: Ztschr. f. klin. Med., **114**, 757, 1930. (15.) **Evans, C. L.**, and **Matsuoka, J.**: J. Physiol., **49**, 378, 1915. (16.) **Gargill, S. L.**: New England J. Med., **209**, 1089, 1933. (17.) **Goldbloom, A. A.**: Internat. Clin., **3**, 206, 1936. (18.) **Goldsmith, G.**: Arch. Int. Med., **58**, 1041, 1936. (19.) **Gordon, J. M.**: Ztschr. f. klin. Med., **68**, 1, 1909. (20.) **Haessler, H.**, and **Newcomer, H. S.**: Arch. Int. Med., **17**, 806, 1916. (21.) **Harrop, G. A., Jr.**: Medicine, **7**, 291, 1928. (22.) **Harrop, G. A., Jr.**, and **Heath, E. H.**: J. Clin. Invest., **4**, 53, 1927. (23.) **Hess, W.**: München. med. Wchnschr., **54**, 1590, 1907. (24.) **Hitzenberger, K.**: Ztschr. f. klin. Med., **126**, 495, 1934. (25.) **Hitzig, W. M.**: Am. Heart J., **10**, 1080, 1935. (26.) **Hofheinz, G.**: Deutsch. Arch. f. klin. Med., **163**, 103, 1929. (27.) **Isaacs, R.**: Arch. Int. Med., **31**, 289, 1923. (28.) **Keith, N. M.**, **Rowntree, L. G.**, and **Geraghty, J. T.**: Ibid., **16**, 547, 1915. (29.) **Liljestrand, G.**, and **Stenström, N.**: Acta med. Scand., **63**, 130, 1925. (30.) **Loewy, A.**: Berl. klin. Wchnschr., **46**, 1393, 1909. (31.) **Lommel, F.**: Deutsch. Arch. f. klin. Med., **92**, 83, 1907. (32.) **Lundsgaard, C.**: J. Exp. Med., **30**, 295, 1919. (33.) **Marsh, H. E.**: Med. Clin. North America, **3**, 741, 1919. (34.) **Meakins, J.**, and **Davies, H. W.**: J. Path. and Bact., **23**, 451, 1920. (35.) **Minot, G. R.**, and **Buckman, T. E.**: Am. J. Med. Sci., **166**, 469, 1923. (36.) **Mohr, J.**: München. med. Wchnschr., **60**, 1739, 1913. (37.) **Morawitz, P.**, and **Röhmer, W.**: Deutsch. Arch. f. klin. Med., **94**, 529, 1908. (38.) **Moritz, F.**, and **v. Tabora, D.**: Ibid., **98**, 475, 1910. (39.) **Resnik, H., Jr.**, and **Friedman, B.**: J. Clin. Invest., **14**, 551, 1935. (40.) **Rover, F.**: München. med. Wchnschr., **58**, 2791, 1911. (41.) **Senator, H.**: Ztschr. f. klin. Med., **60**, 357, 1906. (42.) **Starr, I., Jr.**, and **Gamble, C. J.**: Am. J. Physiol., **87**, 450, 1928. (43.) **Tarr, L.**, **Oppenheimer, D. S.**, and **Sager, R. V.**: Am. Heart J., **8**, 766, 1933. (44.) **Wintrobe, M. M.**: J. Lab. and Clin. Med., **15**, 287, 1929. (45.) **Wright, I. S.**, and **Duryee, A. W.**: Arch. Int. Med., **52**, 545, 1933.

MANOMETRIC DETERMINATION OF THE EFFECTS OF VARIOUS SULFANILAMIDE COMPOUNDS ON BRUCELLA MELITENSIS.

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The rapid development of sulfanilamide derivatives has made it desirable that accurate methods be established for the evaluation of the bacteriostatic or bacteriocidal potency of these drugs. Up to the present time the standard bacteriologic methods for culturing and counting organisms have been used. Such methods have several obvious disadvantages. Constant conditions of O_2 and CO_2 tension, pH and so on, cannot be maintained during the course of the experiment. Observation of growth after transfer of the drug-affected culture to fresh drug-free optimal media tells nothing about the condition of the bacteria during the period of exposure to the drug. The bacteriologic methods of culturing and counting cannot be applied without interrupting the actual experiment. Each time that data are required concerning the effects of the drug upon the bacteria, the original culture tube must be opened, or a separate control culture tube must be used, for determining each single point of the growth curve. It is true that the inaccuracy inherent in variations in the inoculum can be minimized by the use of the photronreflectometer, by which means the initial number of bacteria used for primary inoculation of the culture tubes can be accurately determined, and subsequent comparative determinations of the number of bacteria can be made. No information, however, is obtained by this method as to the state of the bacteria, for the density of cultures may be the same whether the bacteria are living or dead.

The measurement of the chemical reactions of the bacteria by the manometric technique of Warburg[7] is at present the most accurate and sensitive method available for measuring increases or decreases in bacterial metabolism. Such manometric determinations can be carried on for many days with the original culture in the same vessel and, since readings can easily be made every 5 or 10 minutes, the reaction of the bacteria with the drug is continuously observable and quantitative data are available for every

growth period. Constant conditions of O_2 and CO_2 tension, pH, and so on, are maintained throughout the experiment and there is no variation of the bacterial density in different layers of the cultures. Furthermore, the actual reactions of the bacteria are measured during the period of exposure to the drug, thus simulating conditions analogous to those existing *in vivo* during a period of drug administration.

In view of the differences in the effectiveness of the various sulfanilamide compounds with regard to different species of bacteria and different strains of the same species, it seems desirable to try to obtain exact quantitative data on as many single bacterial strains as possible. In this paper we are reporting only that part of our work which deals with the effect of various sulfanilamide compounds on a strain of *Brucella melitensis* var. melitensis. (For complete bibliography on the action of sulfanilamide and allied compounds on brucella, see Long and Bliss;[3] Mellon, Gross and Cooper;[4] Menefee and Poston;[5] Green.[1])

Technique. The strain of *Brucella melitensis* used was obtained from Dr. I. F. Huddleson. Beef infusion—m/28 to m/40 phosphate pH 7.4—broth and human serum of normals and of patients were used as culture media. The age of the bacteria inoculated was from 10 to 120 hours. The culture density at the beginning of the experiment was varied between 100,000 to 40 million organisms per cc. The high density was chosen to shorten the duration of the experiments and to test the difference in effectiveness of the various drugs with regard to maximal infections. Two cubic centimeters of the bacteria-broth-phosphate suspension were pipetted into conical manometer vessels of about 18 cc. capacity and drug solutions (0.07 to 0.14 cc.) were added to make final concentrations of 0.5 to 10 mg. per 100 cc. The oxygen concentration was that of air. The side bulbs of the vessels contained KOH to absorb the carbon dioxide. The manometers were placed in a thermostat at 38° C. and shaken at a rate of 80 to 220 oscillations per minute. Readings were made without stopping the manometers, and the oxygen consumption was measured and calculated according to Warburg.[7] The density determinations were made with the photronreflectometer (Libby[2]). The weight of the bacteria was determined according to Peschel.[6]

We found the dry weight of 100 million organisms to be about $\frac{1}{10}$ mg., the average oxygen consumption of 1 mg. dry weight of *Brucella melitensis* in phosphate broth pH 7.4/ air per hour, $QO_2 = 168$ c.mm.; of 100 million brucella organisms per hour, $\frac{O_2 \text{ consumption}}{100 \text{ million organisms} \cdot \text{hour}} = 1.4$ c.mm. (40 determinations).

The drugs tested were: sulfanilamide (p-aminobenzene-sulfonamide, Merck), sulfapyridine sodium (sodium 2-sulfanilyl aminopyridine monohydrate, Merck), sulfathiazol (2-sulphanilamido-thiazol, Winthrop), sodium disulon (sodium sulfanilyl sulfanilamide, Alba Pharmaceutical Co.), benamide (p-caproylaminobenzene-sulfonhydroxamide, Sharpe & Dohme), promin (sodium salt of p,p′-diaminodiphenylsulfone-N,N′-di(dextrose sulfonate, Parke, Davis Co.), sulfamethylthiazol (2-sulphanilamidomethylthiazol, Winthrop).

Results. Figure 1 illustrates a typical experiment on the effect of sulfanilamide, sulfapyridine sodium, sulfathiazol and sulfamethyl-

thiazol, in concentrations of 5 mg. per 100 cc. each, on the rate of growth of a phosphate broth culture of the Huddleson strain of *Brucella melitensis*. The initial bacterial density as determined by the photronreflectometer was 30 million organisms per cc., so that each of the 5 test vessels contained 60 million organisms (2 cc. suspension).

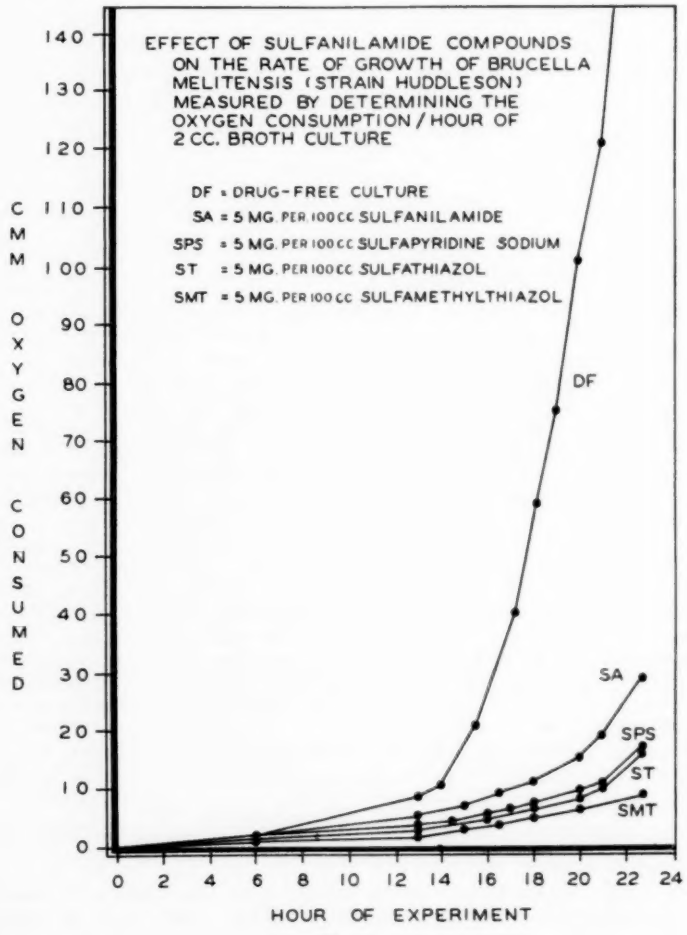
EFFECT OF SULFANILAMIDE COMPOUNDS ON THE RATE OF GROWTH OF BRUCELLA MELITENSIS (STRAIN HUDDLESON) MEASURED BY DETERMINING THE OXYGEN CONSUMPTION / HOUR OF 2 CC. BROTH CULTURE
DF = DRUG-FREE CULTURE
SA = 5 MG. PER 100 CC. SULFANILAMIDE
SPS = 5 MG. PER 100 CC. SULFAPYRIDINE SODIUM
ST = 5 MG. PER 100 CC. SULFATHIAZOL
SMT = 5 MG. PER 100 CC. SULFAMETHYLTHIAZOL
C MM OXYGEN CONSUMED
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140
0 2 4 6 8 10 12 14 16 18 20 22 24
HOUR OF EXPERIMENT
DF
SA
SPS
ST
SMT

FIG. 1.

According to the average metabolism figures of 1.4 c.mm. O_2 per hour for 100 million brucella organisms, as given above, the culture in each vessel should have shown an oxygen consumption per hour of

$$1.4 \cdot 2 \cdot \frac{30}{100} = 0.84 \text{ c.mm. } O_2,$$

provided no growth took place. During the first 12-hour period of the experiment the average oxygen consumption per hour was as follows:

Drug-free culture	1.77 c.mm. O_2
Sulfanilamide culture	1.72 c.mm. O_2
Sulfapyridine sodium culture	1.77 c.mm. O_2
Sulfathiazol culture	1.64 c.mm. O_2
Sulfamethylthiazol culture	0.94 c.mm. O_2

It is, then, evident that some growth did occur in each of the cultures as early as within the first 12 hours. The rate of growth was the same in the sulfanilamide, sulfapyridine sodium, and sulfathiazol cultures as in the drug-free control; whereas in the sulfamethylthiazol culture, even at this early stage, growth was definitely inhibited. Compared to the oxygen consumption of the initial 60 million organisms, the oxygen consumption in sulfamethylthiazol was only increased by 12%, in the 4 other cultures by 95 to 111%.

Eighteen hours after the beginning of the experiment, the differences between the drug-free and the drug-containing cultures appeared more clearly. The oxygen consumption per hour was:

Drug-free culture	59.00 c.mm. O_2
Sulfanilamide culture	10.80 c.mm. O_2
Sulfapyridine sodium culture	7.85 c.mm. O_2
Sulfathiazol culture	6.80 c.mm. O_2
Sulfamethylthiazol culture	4.97 c.mm. O_2

i. e., in the drug-free control it was 70 times as high as at the beginning of the experiment—59 against 0.84 c.mm. O_2 per hour—in sulfanilamide 12.9 times, in sulfapyridine sodium 9.35 times, in sulfathiazol 8.1 times, in sulfamethylthiazol 5.9 times as high. That means that after an observation period of 18 hours, the inhibition of the brucella growth rate was: by sulfanilamide of 81.7%, by sulfapyridine sodium of 86.7%, by sulfathiazol of 88.5%, by sulfamethylthiazol of 91.6%.

In the 23d hour the absolute figures of oxygen consumption per hour were:

Drug-free culture	210.0 c.mm. O_2
Sulfanilamide culture	28.8 c.mm. O_2
Sulfapyridine sodium culture	17.2 c.mm. O_2
Sulfathiazol culture	16.0 c.mm. O_2
Sulfamethylthiazol culture	8.5 c.mm. O_2

i. e., the oxygen consumption per hour in the drug-free control was 250 times higher than at the beginning of the experiment, in sulfanilamide 34.3 times, in sulfapyridine sodium 20.5 times, in sulfathiazol 19.1 times, in sulfamethylthiazol only 10.1 times higher. Using an identical concentration of 5 mg. per 100 cc. for the four drugs, the inhibiting effect of sulfapyridine sodium was 67% greater than that of sulfanilamide, the effect of sulfathiazol 7% greater than that of sulfapyridine sodium, the effect of sulfamethylthiazol

88% greater than that of sulfathiazol, 102% greater than that of sulfapyridine sodium, and 240% greater than that of sulfanilamide.

The cell counts measured with the photronreflectometer at the end of the experimental period of 23 hours, were as follows:

Drug-free culture	12,960 million organisms
Sulfanilamide culture	1,990 million organisms
Sulfapyridine sodium culture	1,035 million organisms
Sulfathiazol culture	960 million organisms
Sulfamethylthiazol culture	580 million organisms

A comparison of the percentage inhibition of growth as determined by the photronreflectometer count (I) and by the manometric measuring of the oxygen consumption (II) shows the results obtained by the two methods in close agreement at this stage of the reaction of the brucella culture with the drugs.

	I.	II.
Sulfanilamide	84.6	86.3
Sulfapyridine sodium	92.0	91.8
Sulfathiazol	92.6	92.4
Sulfamethylthiazol	95.5	96.0

That means that at this stage of the experiment the oxidative metabolism of the brucella organisms is in no way affected by these drugs, but only the rate of growth. The growth-inhibiting effect on brucella, therefore, cannot be explained, as has been suggested (Long and Bliss[3]) by an indirect effect *via* inhibition of processes that sustain the energy supply of the bacteria, but must be interpreted as a direct effect of the drug on factors concerned with cellular multiplication. The first effect of these drugs is "sterilization" of the bacteria, which leaves their life-sustaining metabolic reactions unchanged.

Another effect of sulfamethylthiazol, however, besides this first effect of inhibiting bacterial growth, becomes apparent when the experiment is carried on over a longer period. This effect could not have been found with the density determinations alone without applying the cell physiologic methods. They show that, in contrast to the other drugs tested on this strain of brucella, sulfamethylthiazol not only inhibits the growth of the organisms much more effectively, but that, in addition, it causes a very marked decrease of their metabolism, as evidenced by the dropping of the rate of oxygen consumption per *unit* of bacteria.

Table 1 gives the results of an experiment with a m/40 phosphate pH 7.4 brucella broth culture of an initial density of 32 million organisms per cc. Each manometer vessel contained 2 cc. culture = 64 million organisms. Oxygen consumption and number of bacteria were measured after 24, 28, and 46 hours.

The figures show that not only the total amount of oxygen consumed and the absolute number of bacteria in the culture are smaller in sulfamethylthiazol than in sulfanilamide, but that also the ratio rate of oxygen consumption to unit of bacteria decreases

in sulfamethylthiazol with prolonged action of the drug on the culture. This ratio $\frac{\text{c.mm. } O_2 \text{ consumed}}{100 \text{ million bacteria} \cdot \text{hour}}$ which in all the other cultures examined in this experiment varied between 1.65 and 1.38, is in sulfamethylthiazol after 46 hours only 0.41. The photronreflectometer count shows that between the 28th and 46th hour of the experiment, a comparatively slight but definite increase of the number of bacteria as such has taken place also in sulfamethylthiazol, the increase being 177%. The determination of the oxygen consumption does not only fail to show this increase, but reveals a decrease of 20% instead. This indicates that at this stage of the experiment, either all the bacteria that do grow under exposure to sulfamethylthiazol are impaired by 70% as to their metabolic activities, or that of the 1490 million organisms counted in the sulfamethylthiazol culture after 46 hours, only 450 million organisms are actively alive, whereas 1040 million organisms have ceased to carry out their life-sustaining chemical reactions and, from the point of view of bacterial physiology, must be considered dead.

TABLE 1.—EFFECT OF 5 MG. PER 100 CC. SULFANILAMIDE AND 5 MG. PER 100 CC. SULFAMETHYLTHIAZOL ON CELL COUNT AND METABOLISM OF 2 CC. OF A M/40 PHOSPHATE pH 7.4 BROTH CULTURE OF BRUCELLA MELITENSIS. INITIAL DENSITY: 32 MILLION ORGANISMS PER CC. 38° C. AIR.

Culture.	Hours after beginning of experiment.	C.mm. O_2 consumed per hour.	Number of bacteria, 100 million.	C.mm. O_2 consumed. 100 million bacteria · hour.
Drug-free	24	181.5	120.0	1.51
	28	332.0	236.0	1.41
5 mg. per 100 cc. sulfanilamide	24	22.0	14.0	1.57
	28	55.8	40.5	1.38
	46	684.0*	414.0	1.65
5 mg. per 100 cc. sulfamethylthiazol	24	6.4	4.35	1.47
	28	7.66	5.39	1.42
	46	6.1†	14.9	*0.41*

* Measured after diluting with new broth.
† Measured both in original culture and after diluting with new broth.

Since the injurious effects of bacteria are coupled with their metabolic reactions, such a marked decrease in the metabolic reactions as found in the sulfamethylthiazol culture must lead to a corresponding decrease in the injurious effects on the host. Expressed in terms of practical therapeutics: sulfamethylthiazol not only, through its retarding action on the brucella growth, gives the body a better opportunity to avail itself of its own bactericidal power, but also, when allowed sufficient time for reaction, brings about direct qualitative changes causing irreversible damage to the individual bacteria.

Such gradual dying off of a brucella culture through prolonged action (86 hours) of sulfamethylthiazol is illustrated in Figure 2 by the decrease of the bacterial metabolic activity after a short initial period of increase, as revealed by the rate of oxygen consumption per hour of the culture.

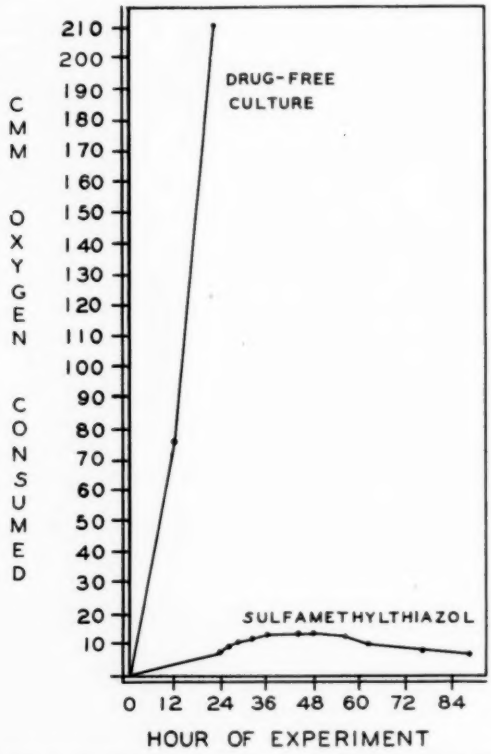

FIG. 2.—Effect of prolonged action of 5 mg. per 100 cc. sulfamethylthiazol on the rate of oxygen consumption per hour of 2 cc. broth culture *Brucella melitensis* (strain Huddleson).

Table 2 gives a comparison of the effect of various sulfanilamide drugs in concentrations of 5 mg. per 100 cc. on the brucella strain. We found the rate of oxygen consumption per hour after 29 hours, in the drug-free culture 185 times greater than at the beginning of the experiment, in promin 116 times greater, in benamide 95.6 times, in sulfanilamide 41 times, in sulfapyridine sodium 17 times, in sulfathiazol 11 times, in sodium disulon 6.4 times, in sulfamethylthiazol 3.8 times greater. That means, the inhibition as against the drug-free control was in promin of 44%, in benamide of 48%, in sulfanilamide of 78%, in sulfapyridine sodium of 91%, in sulfathiazol of 94%, in sodium disulon of 96.5%, in sulfamethylthiazol of 98%.

TABLE 2.—EFFECT OF EQUAL CONCENTRATIONS (5 MG. PER 100 CC.) OF VARIOUS SULFANILAMIDE COMPOUNDS ON CELL COUNT AND METABOLISM OF 2 CC. OF A M/28 PHOSPHATE pH 7.4 BROTH CULTURE OF BRUCELLA MELITENSIS. INITIAL DENSITY 40 MILLION ORGANISMS PER CC. 38° C.

Culture.	Hours after beginning of experiment.	C.mm. O_2 consumed per hour.	Number of bacteria, 100 million.	C.mm. O_2 consumed. 100 million organisms · hour.
Drug-free	29	207.0	178	1.16
Promin	29	129.5	155	0.835
Benamide	29	107.0	94	1.14
Sulfanilamide	29	45.8	36	1.27
Sulfapyridine sodium	29	19.0		
	45	165.0	153	1.08
Sulfathiazol	29	12.3	15.4	0.8
Sodium disulon	29	7.2		
	45	11.5		
	69	58.6		
Sulfamethylthiazol	29	4.3		
	45	5.0		
	69	4.3		
	77	3.4	13.2	0.26

After 45 hours the sulfapyridine sodium culture, as the table shows, has so to speak overcome the inhibition by the drug; activity and quantity of the culture are now about as high as they were in the drug-free control after 24 hours. The inhibiting effect of sodium disulon and sulfamethylthiazol is still undiminished after 45 hours; but 24 hours later, 69 hours from the beginning of the experiment, the inhibiting effect of sodium disulon too has been overcome by the bacteria, and only sulfamethylthiazol still displays its full inhibitory power. Even after 77 hours no increase of bacterial activity could be detected in the sulfamethylthiazol culture; on the contrary, the rate of oxygen consumption was definitely decreased, as compared to that found 24 hours after the beginning of the experiment.

Summary. The advantages of the cell physiologic manometric methods for the study of the effect of the sulfanilamide compounds on bacteria are discussed compared with the conventional bacteriologic methods of culturing and counting.

The effect of various sulfanilamide drugs on large inocula of Huddleson's strain of *Brucella melitensis* was examined by measuring manometrically with the Warburg method the oxygen consumption of the culture, and the density with the photronreflectometer Libby. The drugs tested were: sulfanilamide, sulfapyridine sodium,

sulfathiazol, sulfamethylthiazol, sodium disulon, benamide and promin.

All these drugs were found to be effective in retarding growth in *Brucella melitensis*. The order of their effectiveness, in equal concentrations of 5 mg. per 100 cc. in broth cultures, after a period of 29 hours, for example, was: promin inhibited growth by 44%, benamide by 48%, sulfanilamide by 78%, sulfapyridine sodium by 91%, sulfathiazol by 94%, sodium disulon by 96.5% and sulfamethylthiazol by 98%.

The greater effectiveness of sulfamethylthiazol was evident within the first 12 hours of the experiment, when the oxygen consumption in the sulfamethylthiazol culture was only increased by 12%, as compared with an increase of 105 to 111% in sulfanilamide, sulfapyridine sodium, sulfathiazol and in the drug-free control. With longer duration of the drug action, the difference between the inhibitory effect of sulfamethylthiazol and that of the other sulfanilamide drugs became still more apparent. While even in sodium disulon, second to sulfamethylthiazol in effectiveness, the metabolism of the culture was 52 times greater after 69 hours than at the beginning of the experiment, in sulfamethylthiazol it was hardly 4 times as great.

It could be shown that sulfamethylthiazol in a concentration of 5 mg. per 100 cc., besides inhibiting growth, had a direct cell-damaging effect on the brucella strain examined.

REFERENCES.

(1.) **Green, H. N.**: Brit. J. Exp. Path., **21**, 38, 1940. (2.) **Libby, R. L.**: J. Immunol., **34**, 71, 1938. (3.) **Long, P. H.**, and **Bliss, E. A.**: The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds, New York, The Macmillan Company, 1939. (4.) **Mellon, R. R., Gross, P.**, and **Cooper, F. B.**: Sulfanilamide Therapy of Bacterial Infections, Springfield, Charles C Thomas, 1938. (5.) **Menefee, E. E., Jr.**, and **Poston, M. A.**: J. Bact., **37**, 269, 1939. (6.) **Peschel, E.**: Klin. Wchnschr., **9**, 1061, 1930. (7.) **Warburg, C.**: Stoffwechsel der Tumoren, Berlin, Julius Springer, 1926.

PENETRATION OF BLOOD CLOT BY SULFANILAMIDE, SULFAPYRIDINE, SULFATHIAZOLE AND SULFAMETHYLTHIAZOLE.

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DURING a clinical study of the effect of certain recently developed chemotherapeutic compounds on the course of subacute bacterial endocarditis, it appeared desirable to investigate the ability of these

compounds to penetrate blood clot. It is a well established observation that in subacute bacterial endocarditis the organisms in the vegetations are separated from the blood stream only by a thin layer of fibrin. This barrier is, of course, partially broken down from time to time as vegetations break off or multiplying organisms erupt through the surface of the vegetation. However, as a rule, foci of organisms in the deeper layers of the thrombus remain to carry on the infection. If this were not the case spontaneous healing would be the rule instead of the rare exception, for the killing power of the serum bathing the vegetation is usually very high for the organisms located just beneath its surface. In order to understand the mode of action of drugs in subacute bacterial endocarditis it becomes important to know whether the drug can reach the organisms by penetrating the layer of fibrin which ordinarily protects them.

Procedure. Ten cubic centimeters of human blood was withdrawn, allowed to clot and remain clotted for 24 hours. Then 1 cc. of a solution of sulfapyridine was added to the serum and allowed to remain for another 24 hours. The clot was then removed and chemical determinations of the amount of sulfapyridine present were made on both the clot and the serum. The method used was that of Marshall and Bratton. The clot was prepared by washing thoroughly with 30 cc. of distilled water, drying on filter paper and then weighing. Next it was broken up with a stirring rod and boiled in distilled water three times. After each boiling the supernatant was filtered through Whatman No. 2 filter paper into a volumetric flask. When cool the contents were made up to volume with distilled water and a trichloracetic acid filtrate of appropriate dilution prepared according to the method of Marshall and Bratton, the final determination being done on this filtrate. The serum in this experiment yielded 19.5 mg. per 100 cc., and the clot 0.3 mg. per 100 cc., sulfapyridine. The wash water yielded 0.07 mg. per 100 cc. sulfapyridine. In four subsequent determinations no sulfapyridine was found in the wash water and this procedure was therefore eliminated in later experiments.

Similar determinations were made after the clot had stood in sulfapyridine solutions for 24 hours, 5 days and 10 days (see Table 1). No appreciable penetration of the clot was observed under any of these circumstances.

TABLE 1.—RELATIVE CONCENTRATIONS OF VARIOUS DRUGS IN SOLUTIONS AND IN BLOOD CLOTS AFTER SUSPENSION FOR 24 HOURS, 5 DAYS AND 15 DAYS.

Drug.	Blood. (cc.).	Clot. (hrs.).	Time in sol. (hrs.).	Drug in sol. mg. per 100 cc.	Mg. of drug in clot.
Sulfapyridine	2	72	24	10.0	0
Sulfathiazole	2	48	24	16.3	0
Sulfamethylthiazole	2	48	24	17.2	0
Sulfanilamide	2	48	24	16.1	0.2
Sulfapyridine	2	72	120	10.0	0
Sulfathiazole	2	72	120	14.5	0
Sulfamethylthiazole	2	72	120	14.3	0
Sulfanilamide	2	72	120	23.6	0
Sulfapyridine	2	72	240	10.0	0
Sulfathiazole	2	72	360	17.1	0
Sulfamethylthiazole	2	72	360	18.0	0.2
Sulfanilamide	2	72	360	Hemolysis	Hemolysis

Blood clots were likewise suspended in solutions of sulfanilamide, sulfathiazole and sulfamethylthiazole for 24 hours, 5 days and 15 days. Again, no appreciable penetration of the clot was observed (Table 1).

A fibrin clot was prepared by centrifuging 10 cc. of freshly drawn blood at high speed. The superficial white clot which formed was removed after 72 hours and suspended in a solution of sulfapyridine for 24 hours. The solution yielded 27 mg. per 100 cc. sulfapyridine, the clot none (Table 2).

As a control 1 cc. of sulfapyridine solution was added to 10 cc. of freshly drawn blood which was then allowed to clot and remain clotted for 24 hours. Determinations on the serum yielded 11.8 mg. per 100 cc. sulfapyridine; on the clot 7.9 mg. per 100 cc. (Table 2). This is in accord with Finland's observation that sulfapyridine is distributed throughout the body water both intracellularly and extracellularly in approximately equal amounts.

No.	Blood.	Clot.	Time in S.P. sol.	S.P. in solution, mg. per 100 cc.	S.P. in clot, mg. per 100 cc
1	10 cc.	24 hrs.	24 hrs (serum)	19.5 mg. 100 cc. serum	0.3
2	Fibrin 10 cc.	72 hrs.	24 hrs.	27	0
3	Sulfapyridine added before clotting		24 hrs. (serum)	11.8 mg. 100 cc. serum	7.9

TABLE 2.—SULFAPYRIDINE PENETRATION OF BLOOD CLOTS.

No. 1. Relative concentration of sulfapyridine in serum and blood clot after 24 hours' contact.

No. 2. Relative concentration of sulfapyridine in an acellular fibrin clot and in the solution in which it was suspended for 24 hours.

No. 3. Relative concentration of sulfapyridine in serum and in a blood clot when sulfapyridine was added before clotting occurred.

Discussion. These experiments afford an explanation for some of the apparent discrepancies between the bactericidal effect of sulfanilamide and allied compounds *in vitro* and their therapeutic effectiveness in subacute bacterial endocarditis. Even in those cases in which the drug is actively bactericidal for the causative organism, it is probably prevented from coming into contact with it by an impenetrable layer of fibrin. This does not mean, however, that complete eradication of the infection is theoretically impossible. In the course of time all of the preëxisting thrombi should become organized into fibrous scar tissue while all newly formed thrombi in a patient under active treatment will be impregnated with the drug. Thus conditions will tend to become less and less favorable for growth of the organism if an effective drug is taken continuously over a long period of time.

Summary. Human blood clots suspended in solutions of sulfanilamide, sulfapyridine, sulfathiazole and sulfamethylthiazole for periods of 24 hours to 15 days did not show any appreciable penetration by the drugs. The inferences to be drawn from these observations in relation to the chemotherapy of subacute bacterial endocarditis are discussed.

THROMBOCYTOPENIC PURPURA DUE TO SULFAPYRIDINE.

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Recent medical literature contains many reports of agranulocytosis and severe hemolytic anemia caused by sulfapyridine. There have been no reports of thrombocytopenic purpura caused by this drug. It seems worthwhile that 2 cases of this disease caused by sulfapyridine should be reported.

Case Abstract. Case 1.*—M. R., a negro, aged 41, developed chills and fever 4 days prior to admission to the hospital. On admission, the temperature was 104° F. Physical examination showed evidence of consolidation of the left lower lobe and a few râles in the left upper pulmonic area. Roentgen ray showed pneumonitis of the left lower lobe and a cavity in the left upper lobe. The day after admission, acid-fast bacilli were found in the sputum. No pneumococci were found. Another Roentgen ray 4 days later showed extension of the process in the left lung. During the first 10 days in the hospital he received 4.5 gm. of sulfapyridine daily (total dose of 45 gm.). Ten days after admission he developed hemoptysis and recurrent epistaxis. The drug was discontinued. On the eleventh day he developed a generalized purpura involving the entire body and the epistaxis and hemoptysis became continuous. He also developed oozing from the gums. On transfer to the Tuberculosis Service at Grasslands Hospital, he had generalized purpura, profuse bleeding from the mucous membranes of the mouth and nose with large adherent clots filling the mouth and nasal passages. The heart rate was 130, rhythm regular, no murmurs. There was dullness with increased vocal fremitus and resonance throughout the left chest. A record of the blood picture on admission and subsequently is given in Table 1. Included in this table also is a record of transfusions.

A diagnosis of thrombocytopenic purpura was made.

It was suggested that the patient receive multiple transfusions, intravenous vitamin C, 1000 mg. daily, local application of fer de lance venom to bleeding areas.

The day after admission he received 550 cc. of whole blood and the bleeding from the mucous membranes subsided. He continued to have purpuric manifestations for 5 days after the first transfusion. Ten weeks after receiving sulfapyridine he developed progressive jaundice without fever or pain. The feces remained highly colored. The area of liver dull-

* Case "M. R." is presented through the courtesy of Dr. W. G. Childress, Physician in Charge, Division of Tuberculosis and Diseases of the Chest, Grasslands Hospital.

TABLE 1.—M. R.

Date.	R.B.C. (mill. per c.mm.).	W.B.C.	Hgb., (%).	Newcomer (gm.).	Differential leukocyte count. St.	Seg.	Lym.	Mono.	Eosin.	Bas.	Plat.	Sputum.	N.P.N.	Transfusion (cc.).
12/10/39	3.74	6550	73	12.5	0	84	15	1	0	0	60,000	..	54.5	550
12/11	3.01	6900	65	11.0	..	..	..	..	..	..	....	..	..	600
12/12	3.41	5050	56	9.4	19	56	15	10	0	0	34,000	Neg.	..	
12/16	3.78	..	71	12.0	..	..	..	..	..	..	123,000			
12/19	2.74	8400	60	10.2	..	..	..	..	..	..	183,000	..	..	300
12/21	3.18	9350	68	11.5	..	..	..	..	..	..	178,000	+	29.0	300
12/26	4.08	6900	65	11.0	11	61	23	5	0	0	205,000			
1/7/40	4.10	8400	73	12.5	..	..	..	..	..	..	300,000	+	Icterus index	
2/4	4.50	7200	76	13.0	0	64	31	5	0	0	310,000		2/29/40	75
3/2	4.20	4800	76	13.0	..	..	..	..	..	..	311,000	Neg.	3/5	64
3/7	4.40	8200	82	14.0	18	56	24	0	2	0	501,000	Neg.	3/13	27
4/9	5.50	8000	90	15.0	16	60	20	4	0	0	....	Neg.	3/19	19

TABLE 2.—F. N.

Date (1940).	R.B.C. (mill. per c.mm.).	W.B.C.	Hgb., (%).	Newcomer (gm.).	Differential leukocyte count. St.	Seg.	Lym.	Mono.	Eosin.	Bas.	Plat.	Hematocrit.	Transfusion (cc.).	Bleeding time (min.).	Coagulation time (min.)
2/8	4.40	6,000	74	12.3	11	62	19	8	0	0	App. norm.				
2/18	3.89	7,650	64	10.88	..	..	..	..	..	..	7,780	..	500	17	7
	4.26*		72	12.24							12,780				
2/19	3.34	8,000	58	9.86	17	59	16	5	2	1	....	..	600	21	7½
2/20	3.61	5,050	53	9.01	18	60	14	6	1	1	3,610	29%	600	51	6
2/21	2.85	8,950	45	7.65	..	..	..	..	..	..	1,425	20%	....	47	9
2/22	0.98	19,000	11	1.87	..	..	..	..	..	..	None seen	..	..	184	

* After transfusion.

ness appeared decreased by approximately 40%. He was given a high carbohydrate diet, 200 cc. of 25% glucose intravenously daily and 5 mg. of thiamin chloride orally three times a day. The curve of the icterus index indicates the rate at which the jaundice disappeared. As the jaundice subsided his appetite increased. Pneumothorax treatments were instituted and the tuberculous process which had involved both apices has shown marked regression.

Other laboratory tests performed were: Kline, negative; blood sulfapyridine on admission, 2.9 mg. per 100 cc.; serum albumin, 3.9; serum globulin, 2.7; total protein, 6.6; phosphorus, 4.1; phosphotase, 6.2 Bodansky units; galactose tolerance test showed results within the limits of normal; prothrombin clotting time 89% of normal.

CASE 2.—F. N. The patient was an Italian-born white man of 60. He had measles and whooping cough during childhood. The family history was without record of value. Three days prior to admission he d veloped a sore throat, fever, pain in the chest, dyspnea, and a non-productive cough. Physical examination revealed a well-nourished white male showing marked dyspnea. The throat was inflamed and there was mucopurulent exudate over the pharyngeal wall. Examination of the chest showed dullness with diminished breath sounds and moist râles at the base of the left lung. The heart was normal. The abdomen presented no abnormalities and neurologic examination showed nothing abnormal. The blood pressure was 120/80. Roentgen ray of the chest on the day of admission showed consolidation of the left base. A Roentgen ray diagnosis of lobar pneumonia was made. The temperature on admission was 103.2° F. and 4 hours later rose to 104° F. At that time he was given sulfapyridine and received 18 gm. in the next 4 days. The temperature dropped in 24 hours to 100.8° F. and on the fourth day was normal. The drug was discontinued on the fourth day because of hematuria. This was followed by a rise in temperature to 102.4° F. and during the next 3 days he received an additional 5 gm. of sulfapyridine. This caused a fall in temperature to 100° F. He received a total of 23 gm. of the drug.

Sputum typing showed no pneumococci Types I to XXXIII either by Neufeld reaction or mouse inoculation. Pneumococci of a higher type were present. Sputum culture showed a few pneumococci; 60% *Staph. albus* and 30% hemolytic streptococci. Throat culture showed 70% hemolytic staphylococci and 30% hemolytic streptococci. His blood picture is given in Table 2.

The urine after 4 gm. of sulfapyridine had been given showed albumin 1+; a few fine and coarse granular casts; 15 to 20 R.B.C. per high-power field.

Two days after admission a throat irrigation showed much mucous streaked with blood. Six days after admission another urinalysis showed 1+ albumin; occasional coarse granular casts; 40 to 50 R.B.C. per high-power field. Seven days after admission he developed epistaxis which lasted 6 hours despite energetic treatment. On the eighth day of hospitalization he developed purpuric manifestations in the skin of face and extremities. Recurrent bleeding from the nose continued. The next day he developed bleeding from the gums and mucous membranes of the mouth. Large ecchymotic areas appeared on the skin of extremities and trunk. Blood studies established a diagnosis of thrombocytopenic purpura and the results are recorded in Table 2.

The patient began to pass bulky tarry stools. The pulse became rapid and diffuse perspiration developed. The patient received three transfusions totalling 1700 cc. of whole blood with very little effect on the bleeding

* After transfusion.

tendency. He also received cevitamic acid, 150 mg. orally, daily; intravenous injections of oxalic acid 5 mg. twice daily without appreciable effect on the bleeding. On the day of his death, the bleeding time was 3 hours, 4 minutes and no blood platelets could be found in the stained smears. He died 14 days after admission. Autopsy could not be obtained.

Bone marrow biopsy showed the following differential:

	Per cent.	
Myeloid cells:		
Undifferentiated cells	1.0	
Myeloblasts	1.1	
Premyelocytes:		
Neutrophils	3.0	
Eosinophils	2.0	
Basophils	0.5	
Myelocytes:		
Neutrophils	9.1	
Eosinophils	6.3	
Basophils	1.1	
Metamyelocytes:		
Neutrophils	6.1	
Eosinophils	3.2	
Basophils	0.0	
Segmented forms:		
Neutrophils	3.1	
Eosinophils	2.8	
Basophils	0.0	
		39.3
Erythroid cells:		
Megaloblasts	3.4	
Macronormoblasts	33.2	
Normoblasts	18.5	
Megakaryocytes	3.5	
Lymphocytes	1.9	
Plasma cells	0.2	
		60.7
		100.0

The only significant changes from normal in the cellular studies of the bone marrow are the moderate increase in megakaryocytes and a definite increase in the nucleated red blood cells. The increase in the latter is undoubtedly due to a response on the part of the bone marrow to the loss of blood.

Conclusion. Two cases of thrombocytopenic purpura developing during the course of treatment with sulfapyridine are reported. One case also showed evidence of acute toxic necrosis of the liver. The disease was fatal in 1 case. A bone marrow biopsy study in this case is reported.

It seems advisable that patients receiving sulfapyridine should be under close observation with frequent studies of the peripheral blood and frequent examinations of the urine. As soon as toxic manifestations develop the drug should be discontinued.

POSTPUBERTAL MENORRHAGIA AND ITS POSSIBLE RELATIONS TO THROMBOCYTOPENIC PURPURA HEMORRHAGICA.

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Thrombocytopenic purpura hemorrhagica apparently of the idiopathic type may develop in association with menstrual disturbances, the circumstances being such as to suggest more than mere coincidence. It is now known that in the majority of women there is a physiologic decrease in the number of platelets in the circulating blood in the 2 weeks preceding menstruation, the low point being reached on the first menstrual day.[11] This helps to throw light on those interesting patients whom Minot described under the title of "Intermittent Menstrual Types of Purpura Hemorrhagica with Lymphocytosis."[8] The old observation that some women bruise more easily before their menstrual period seems to have a definite basis. Certainly menorrhagia may be the most important of a number of hemorrhagic phenomena caused by thrombocytopenia.[4] It is seldom realized, however, at least in this country, that severe menorrhagia may be the only symptom of essential thrombocytopenic purpura. Recent reports from various European clinics indicate that this occurrence is not altogether rare and that instances of serious or even fatal menstrual hemorrhage are likely to have such an origin.[6,13] Israel and Mendell[5] recently reported a case in which splenectomy was necessary to halt serious menorrhagia. C. T. Smith[12] also noted the importance of blood platelet counts in girls who at puberty show hemorrhagic tendencies, with menstrual hemorrhage an outstanding feature. We wish to report herein the development of idiopathic thrombocytopenic purpura in a young girl whose only symptom was severe menorrhagia. Splenectomy was curative. We have included abstracts of histories of: 1, another girl with menorrhagia of puberty with moderate thrombocytopenia; and 2, a woman who suffered from menorrhagia since puberty, developing in later years the complete clinical picture of essential thrombocytopenic purpura.*

* We are able to include this interesting case through the kindness of Dr. Thomas Klein of the Philadelphia General Hospital.

Case Abstracts. CASE 1.—H. T., a 14-year-old girl, was first admitted to the Jewish Hospital on June 9, 1939, on the service of Dr. Joseph Doane, and later studied by Dr. Mitchell Bernstein. The patient began to menstruate when 12½ years old. The first 6 periods occurred regularly on a 28-day cycle, each lasting 5 days. Thereafter, they were irregular, delayed once for 3 months, during which time a few spots, possibly purpuric, appeared in the skin of the knees and elbows. They disappeared in a few days. Otherwise, neither undue ecchymosis nor other hemorrhagic changes were ever noted. In June, 1939, shortly after the onset of an irregular menstrual period, profuse uterine hemorrhage began, which soon caused an acute anemia with marked pallor and weakness. On admission to the hospital the patient's erythrocyte count was 2,000,000 and the Hgb. 31%.

A total of 16 blood transfusions had to be given in almost daily sequence before the hemorrhage was definitely controlled. It did stop on June 22, but recurred on the 26th and continued profusely into the first week of July. The hemoglobin which had risen to 93% fell back to 43%. Following a brief respite, another hemorrhage of 4 days' duration occurred. It was not clear whether these recurrences were really menstrual periods. Before and in both of them large doses of progesterone, 5 mg. intramuscularly, were given almost daily. This, plus the daily administration of 200 rat units of antuitrin S for 7 days in conjunction with the numerous transfusions, finally controlled the hemorrhage. Which of these measures was responsible could not be determined. The patient was discharged on July 19th with the diagnosis of uterine hemorrhage due to progesterone deficiency, based on the report of Dr. S. Levine who in an endometrial biopsy noted "absence of progesterone activity." Numerous tests appeared to exclude at that time the possibility of a blood dyscrasia. The blood platelet count was 150,000, the bleeding and coagulation times were normal, each being 4 minutes.

The patient did not bleed at home for 3 weeks, although receiving no treatment. Prior to the onset of menstruation in August she received "prophylactically" 5 daily intramuscular injections, each 5 mg., of progesterone (proluton, corpus luteum extract). A profuse menstrual hemorrhage began, necessitating readmission to the hospital on August 24, on the service of Dr. Harold Goldburgh. At this time there was a mild fever, tachycardia and marked anemia. The erythrocyte count was 2,100,000 and the Hgb. 30%. In contrast with previous findings the bleeding time was greatly prolonged, being more than 20 minutes, and the platelet count was 2000. The coagulation time was 2½ minutes and the erythrocyte fragility zones were normal. Other laboratory tests were negative. The Rumple-Leeds test was negative despite the scarcity of blood platelets, the tourniquet being left on the arm for 10 minutes without the appearance of a single petechial mark.

There was nothing else of note in the examination. The girl was well developed and apparently free of any infection that could be relevant to the hemorrhagic state. A pelvic examination revealed no abnormality. Neither the superficial lymph nodes nor the spleen were palpable, although the latter was thought to be enlarged by percussion.

It was thought that endocrine dysfunction was the important cause of the menorrhagia and therapy was carried out accordingly. The patient received 1750 cc. of blood in 5 transfusions in the first week of hospitalization. Progesterone, 5 mg. per day, was given intramuscularly for 1 week and shortly afterward in 10 mg. doses each day for 9 days. Following this, we administered 30 mg. in 2 days without any beneficial effect on the bleeding then occurring, or on the low platelet counts. A little later progesterone was again given in 5 mg. doses almost daily for 22 days. Anterior pituitary-like hormone was used intermittently, finally in 2 cc. doses,

3 times per week for 1 month. Irradiation of the pituitary and of the ovaries was carried out as suggested by the gynecologic and radiologic consultants, but without any definite clinical effect. The local use of radium for metromenorrhagia was suggested as a palliative measure, but was rejected for various reasons.

The erythrocyte count was gradually elevated, apparently as a result of the many transfusions, so that on October 5 it was 5,000,000 with 90% hemoglobin. Nevertheless, the platelet count remained constantly low, coming up from the originally very low counts of 2000 and 3000 to a level of about 25,000. The uterine hemorrhage slackened but recurred with such frequency as to rule out at this time any dependence on a menstrual cycle. Very few days were free of hemorrhage and with the cessation of blood transfusions repeatedly sharp drops in hemoglobin occurred, threatening the development of a chronic anemia. Eventually, on October 16, the tourniquet test was positive, numerous purpuric spots appearing within 3 minutes; on October 21, purpura was noted on both legs.

On October 21, Dr. Edward Steinfield reported on a sternal bone marrow biopsy. He found adequate erythropoiesis and granulopoiesis. Normal maturation of those series was noted. No megakaryocytes were seen which, in view of the thrombocytopenia, was considered indicative of a depressed thrombocyte formation.

On October 25, splenectomy was performed by Dr. Frank Block. The spleen was not weighed, but it was moderately enlarged, measuring 10 by 7½ by 3½ cm. Dr. Levine later found changes indicative histologically of thrombocytopenic purpura.[9]

The result was decisive. The preoperative platelet count was 22,200. At noon, October 25, immediately after the operation, the count was 29,000; at 3 P.M. it was 45,000, and on the next day, *i. e.*, the first postoperative day, the count rose to 137,000. On November 1, it was 810,000, followed thereafter by a gradual decline to more normal figures. The bleeding time on the first postoperative day was reduced to 4½ minutes and on November 1 (the sixth postoperative day) it was 1½ minutes. Vaginal bleeding continued for 4 postoperative days, gradually diminishing, and then ceasing altogether. Endocrine therapy had been discontinued shortly before operation.

The patient was discharged on November 14, with normal blood findings and free of hemorrhage for 16 days.

"Follow up" examination revealed a normal blood status. The blood platelet count on April 10, 1940, was 360,000. Menstruation returned in December, 1939, but has not occurred since then, an amenorrhea of 4 months' duration. There is no evidence of any hemorrhagic tendency.

CASE 2.—K. McG., a 13-year-old white girl menstruated for the first time on May 29, 1937. After a moderate 2-day flow, the menstruation ceased, but returned 2 days later, from which time the patient bled continuously in increasing amounts. She was hospitalized on June 17, at which time she was extremely pale and moderately dyspneic. The hemoglobin was 31%, the erythrocyte count 2,000,000, blood platelets 110,000. The temperature was 100.3°, the pulse rate was 140, and hemic murmurs were heard over the precordium. The patient had previously been in excellent health, had not suffered from any hemorrhagic tendency. There was no history of self-medication. The diagnosis was "functional bleeding due to endocrine disturbance." The patient received 4 transfusions of 250 cc. each in 6 days. On June 23 the platelet count had risen slightly to 128,000. On June 24, menorrhagia stopped, and on June 28, the blood count showed a hemoglobin of 60%, 3,300,000 erythrocytes and 180,000 platelets. The only medication was the daily injection of 2 cc. antuitrin S for a period of 1 week.

The patient was discharged on July 7, 1937, apparently well. Menorrhagia has not recurred. It is of interest, however, that a younger sister, six years old, is now in the hospital with a complete picture of idiopathic thrombocytopenic purpura.

CASE 3.—B. P., a white woman, aged 51, complaining of "hemorrhages over the body," was admitted to the Philadelphia General Hospital on the medical service of Dr. Thomas Klein. She had noted excessive bleeding from small cuts for many years, especially in the last 2 years. In 1938 there was a serious hemorrhage from a tooth socket following dental extraction, and at that time she noted black and blue spots in the skin, appearing first on the legs and later over the entire body. In the last 3 months her body has been covered with recurring purpuric spots.

Her menstruation began at the age of 11. Menstrual bleeding from the beginning was excessive, continuing from 7 to 10 days, and usually so profuse as to confine her to bed for 2 to 3 days because of hemorrhage *per se*. Menorrhagia continued regularly until the age of 38 when menstruation suddenly ceased. On admission to the hospital, the erythrocyte count was 4,210,000, the leukocyte count 5400 and the Hgb. 85%. The blood platelet count was 120,000 and the bleeding time was 14 minutes.

This patient's daughter, aged 27, began to menstruate when 10½ years old. Her menstrual history is identical with that of her mother, featured by marked menorrhagia that has resisted medical treatment. There has been no history of purpura. Unfortunately, the platelet count and bleeding time have not been recorded.

Discussion. It is apparent that idiopathic thrombocytopenic purpura, at first "sans purpura," may occur at puberty or shortly thereafter in association with menstrual irregularities. Milder degrees of the menorrhagia of puberty relieved by blood transfusions as in our Case 2, or terminating spontaneously, are not uncommon. The basis of the association with menstruation remains obscure. In some patients a hemorrhagic tendency was noted in early childhood, reappearing at puberty with severe menorrhagia. Such patients are possibly like those of Minot, precipitated into clinical activity by premenstrual thrombocytopenia. The problem, however, of puberty or postpuberty thrombocytopenic purpura appears to be more complex. Some patients, as in Case 2, never showed a hemorrhagic tendency. Case 1, aside from a few possibly purpuric spots recalled only after persistent questioning, likewise was in excellent health until the advent of menorrhagia. Detailed blood study in this case did not reveal at first any change suggestive of thrombocytopenic purpura. One month later with the recurrence of menorrhagia, the platelets had practically disappeared from the circulating blood and the bleeding time was greatly prolonged. In Case 2 severe hemorrhage continued for 3 weeks; the platelet count was low, 110,000, a level, however, somewhat higher than the severity of the symptoms would suggest if the diagnosis of uncomplicated essential thrombocytopenic purpura was correct. Similarly with Israel and Mendell,[5] the patient had been bleeding for 3 weeks, at which time the platelet count was 190,000, the bleeding time 7 minutes. While the latter was moderately prolonged, the data were not indicative of thrombocytopenic purpura and it was

only after further examination revealed progressive blood changes that the diagnosis could be made. It is clear then that severe menorrhagia at puberty may precede and actually initiate the clinical state of idiopathic thrombocytopenic purpura. One may postulate a "qualitative" deficiency of the platelets which, however, will not explain normal or only slightly prolonged bleeding times in initial examinations. Factors aside from splenic dysfunction may be important. It has been suggested that a relationship exists between the spleen and the female endocrine system, especially that part of it governing menstruation, in which the thrombocytolytic action of the spleen may be unduly stimulated.[10] It is conceivable that a toxic effect leading to destruction of blood platelets or megakaryocytes may be traced to some abnormality in the complicated menstrual cycle.

An experimental Werlhof disease has been produced in dogs by injection of various sex hormones,[1] but this thrombocytolytic effect has never been demonstrated in human beings.[2,14] Charlotte Ehrenberg[3] injected large doses of corpus luteum extract into 2 dogs and observed definite qualitative and quantitative platelet deficiencies within 24 hours. This supported Ehrenberg's belief that corpus luteum therapy may aggravate menorrhagia, as it did in her patient. Unaware of this work, we also felt that corpus luteum was possibly a factor in these cases because its development in the last 2 weeks of the menstrual cycle coincides with the usual reduction in blood platelets. Gynecologic consultants had recommended its use in Case 1 to prevent recurring menstrual hemorrhage. Accordingly, the patient received large injections of progesterone (proluton) on the last 5 premenstrual days. The expected protective action was entirely missing. The patient had to be promptly rehospitalized and at this time the platelet count was 2000. Six daily transfusions finally brought the hemorrhage under partial control, but while the erythrocyte count rose from 2.1 million to 3.5 million and the Hgb. from 30% to 60%, the platelets remained at a low level of 3500, as evidenced by daily counts. The usual postmenstrual rise in platelets did not occur. During this time, the patient received 5 mg. of progesterone every day. Corpus luteum therapy was clearly ineffective and exerted if anything a deleterious effect.

There was, on the other hand, no doubt of the existence in this case of idiopathic thrombocytopenic purpura. While for many weeks menorrhagia was the only hemorrhagic sign, the full picture of purpura, impaired capillary resistance and positive laboratory signs eventually became evident and the results of splenectomy confirmed the diagnosis. This gradual unfolding of the clinical picture may be emphasized as characteristic of puberty thrombocytopenic purpura. The evolution may be delayed for a long time. In the series of cases of Leschke and Wittkower,[7] depicting various types of thrombocytopenic purpura, there is (Case 6) the interesting

example of "monosymptomatic" involvement, a woman aged 23 who since her first menstrual period at the age of 11 suffered severe menorrhagia requiring repeated hospitalization. Purpura did not appear for many years despite the fact that nose bleeding and unduly large bruise marks were noted for a brief time in early childhood. The platelet count, first determined at the age of 22, was 3700. Instead of splenectomy, the surgeon removed the uterus and a cystic degenerated right ovary. Not only was there cessation of menorrhagia, but the nosebleeds noted preoperatively disappeared, notwithstanding the fact that the blood platelet count remained constantly under 3000 and the bleeding time 45 minutes. After 2 postoperative years of apparently restored health, purpura appeared for the first time and impaired capillary permeability was noted. One may speculate on the possibility in such a case of a stimulation of splenic thrombocytolytic activity by a factor inherent in an abnormal menstrual cycle, the stimulation remaining years after surgical removal of the inciting factor. Some of these patients have structural changes associated with menstruation. Case 1 showed a "progesterone" deficiency in endometrial biopsy. The patient of Israel and Mendell had an "atrophic and dysplastic" endometrium.

Finally, a familial tendency to thrombopenia is apparent in some cases. Case 2 is suggestive and in Case 3, while the data remain incomplete, the history is indicative of an inherited tendency. Other cases of serious thrombopenic menstrual hemorrhage almost certainly show this familial trait.[14]

Summary. There is a small group of girls, apparently in otherwise good health, who at the onset of puberty or soon afterwards develop menorrhagia associated usually with irregularities in cycle.

This menorrhagia may be the first indication of idiopathic thrombocytopenic purpura. The deficiency in blood platelets and the increased bleeding time pathognomonic of this disturbance may gradually appear after a variable length of time. Similarly, the appearance of impaired capillary resistance and of spontaneous purpura is delayed for many weeks or months. The medical history may reveal a past hemorrhagic tendency in early childhood which apparently disappeared only to return at puberty as an abrupt and serious menorrhagia.

Splenectomy is curative as far as the hemorrhagic process is concerned, and is indicated in those cases where repeated blood transfusions and endocrine therapy have failed to check the hemorrhagic tendency and the fall in platelet count.

It is suggested that some abnormality in the menstrual cycle may stimulate the thrombocytolytic activity of the spleen. The exact nature of this interrelationship requires further elucidation. Corpus luteum may be a factor as indicated by its destructive effect

on the blood platelets in experimental work. There is some slight clinical evidence of this effect in patients of the type herein described.

The blood platelets should be counted and the bleeding time determined in every case of menorrhagia in adolescent girls. These tests should be repeated despite initial normal findings if the hemorrhagic process continues.

REFERENCES.

(1.) **Arnold, O., Holtz, F.,** and **Marx, H.**: Naturwissensch., **24**, 314, 1936. (2.) **Benhamou, E.,** and **Nouchy, A.**: Gynec. et obst., **25**, 96, 1932. (3.) **Ehrenberg, C.**: Monatschr. f. Geburtsh. u. Gynek., **51**, 99, 1920. (4.) **Haden, R.**: Principles of Hematology, Philadelphia, Lea & Febiger, 1939. (5.) **Israel, L.,** and **Mendell, T.**: Am. J. Obst. and Gynec., **38**, 339, 1939. (6.) **Koller, T.**: Schweiz. med. Wchnschr., **62**, 913, 1932. (7.) **Leschke, E.,** and **Wittkower, E.**: Ztschr. f. klin. Med., **102**, 649, 1926. (8.) **Minot, G. R.**: Am. J. Med. Sci., **192**, 445, 1936. (9.) **Nickerson, D. A.,** and **Sunderland, D.**: Am. J. Path., **13**, 463, 1937. (10.) **Pfeiffer, R.,** and **Hoff, R.**: Zentralbl. f. Gynek., **46**, 1765, 1922. (11.) **Pohle, F. J.**: Am. J. Med. Sci., **197**, 40, 1939. (12.) **Smith, C. T.**: South. Med. and Surg. J., **94**, 301, 1932. (13.) **Van Vugt, D.**: Nederl. Tijdrschr. v. Geneesk., **2**, 352, 1925. (14.) **Zondek, H.,** and **Kaatz, H.**: Brit. Med. J., **2**, 387, 1936.

ACUTE NEPHRITIS: REVIEW OF 77 CASES.*

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The conception of acute glomerular nephritis as a disease of children which follows severe infections, especially scarlet fever, and is characterized by albuminuria, hematuria, edema, and convulsions has been shown to be inadequate. Due in large measure to the studies of Löhlein,[19] Addis,[1] and Longcope,[20a] its relation to other infections, particularly streptococcal infections of the upper respiratory tract, has been appreciated, and it has become more and more apparent that the renal lesion is only one, albeit usually the most conspicuous one, of the manifestations of the reaction to infection which is called acute nephritis.

While acute nephritis is more common in children than in adults, it may occur at any age. Moreover, not only is the prognosis more serious in the older age groups, but the onset is frequently more insidious and the symptoms less dramatic. The greater number of reports on the symptoms and particularly the prognosis of acute nephritis have been concerned with children. Within the past few years, several reports on the disease in adolescents and adults have appeared. These have emphasized the frequency of apparently mild

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infections of the upper respiratory tract as the precursors of acute nephritis and the high incidence of the subsequent development of chronic nephritis.

This report describes the symptoms and clinical course of 77 cases of acute glomerular nephritis treated in Lakeside Hospital from 1931 to 1939. Table 1 shows the age distribution, sex, color, and incidence per 1000 admissions. The proportion of colored patients (19%) is approximately that of hospital admissions. On the other hand, 81% of the cases of acute nephritis were in males, while they comprise only 43% of admissions. The material is not representative of the incidence of acute nephritis for several reasons. Only the severer cases of acute nephritis were admitted to the wards. The few children included are those admitted to the surgical wards, as these were the only records of children admitted to the University Hospitals that were available for study.

TABLE 1.—YEARLY ADMISSIONS, AGE AND SEX DISTRIBUTION OF 77 CASES OF ACUTE NEPHRITIS.

Year.	Number.	Rate per 1000 admissions.	Age.	Number.
1931	2	0.23	0–10	6
1932	7	0.73	11–20	22
1933	10	1.11	21–30	23
1934	8	0.79	31–40	11
1935	8	0.71	41–50	12
1936	5	0.40	51–60	1
1937	10	0.77	61–70	1
1938	15	1.10	71–80	1
1939	12	0.84		
Total	77			

Male white, 43; colored, 12. Female white, 19; colored, 3.

A history of a preceding infection was obtained in 75 of the 77 cases. Of these, infection of the upper respiratory tract, sinuses, and ears accounted for 56. These etiologic factors are shown in Table 2 where a number of similar studies on adults have been assembled from the recent literature for comparison. Scarlet fever may be regarded as an infection of the upper respiratory tract, and if so grouped, infections of the upper respiratory tract account for 669 (69%) of the collected cases. The incidence of acute nephritis in these infections is, however, low. Kayser-Petersen and Schwab[12] found only 10 instances of acute nephritis in 479 cases of angina. The reported incidence after scarlet fever has varied in different epidemics, from about 5% in McCrae's[22] series to 1.3% in that of Lucchesi and Bowman.[21] Scarlet fever is apparently much less likely to be followed by glomerulonephritis in adults than in children. While the incidence of nephritis following upper respiratory tract infections is thus quite low, the complication may have such serious consequences that its early recognition is of the utmost importance.

The incidence of pneumococcic pneumonia preceding nephritis differs considerably in different reports. Some authors do not report

any cases, while according to others it accounts for 5% to 8% of the cases. Of course, febrile albuminuria is common in pneumonia; a few red cells, particularly in the urine of bacteremic patients, not uncommon. Such findings are probably indicative of a focal nephritis, the result of localized infection in the kidney rather than the allergic response which is recognized as acute diffuse glomerulonephritis. Seegal[30] reported 7 instances of acute nephritis in 1004 cases of pneumonia. Goldring and Wyckoff[9] found 2 patients who developed typical glomerulonephritis, with hematuria, edema, and elevated blood pressure among 44 cases of lobar pneumonia whose kidney function was carefully followed. In these cases, symptoms developed 12 and 13 days after the crisis.

TABLE 2.—PRECEDING INFECTION IN ACUTE NEPHRITIS.

	Murphy and Rastetter.[25]	Leavell *et al.*[14]	Falkers.[6]	Longcope.[20b]	Richter.[27]	Seegal.[31]	Volhard.[33]	Lichtwitz.[16]	Hayman and Martin.	Total.	Per cent.
Number of cases	150	82	68	116	100	218	71	94	77	976	
Sore throat, tonsillitis	21	21	0	68	37	94	17	28	27	313	32.1
Upper respiratory tract	99	10	31	0	27	37	8	9	17	238	24.4
Otitis and sinusitis	0	4	0	21	2	17	0	0	12	56	5.7
Scarlet fever	2	8	6	9	4	9	19	3	2	62	6.4
Skin infections	0	5	5	8	0	0	0	19	3	40	4.1
Pneumonia	0	0	0	0	5	15	6	4	9	39	4.0
Rheumatic fever	1	0	0	4	1	7	2	0	2	17	1.7
Miscellaneous	21	17	6	1	9	22	17	5	3	101	10.3
Infection unknown	6	17	20	5	15	17	2	26	2	110	11.3

Another disease in which the relation to acute nephritis is uncertain is rheumatic fever. While during the febrile stage there is an increased elimination of protein, casts and cells, true glomerular nephritis is certainly uncommon. Baehr and Schifrin[3] found only 3 instances among 235 autopsied cases of rheumatic fever dying during the acute stage, and of these they believed one antedated the rheumatic infection and another was terminal. Loeb[18] and Goldring,[8] however, have reported typical cases, and it was present in 4.7% of cases of rheumatic fever observed by Salvesen.[29] The common microscopic hematuria in rheumatic fever is probably an expression of the hemorrhagic tendency of the disease rather than of glomerular inflammation. The urinary changes must be accompanied by edema or hypertension before a diagnosis of acute glomerulonephritis is justified.

In subacute bacterial endocarditis, in addition to the focal embolic lesion, diffuse glomerulonephritis is not uncommon, while in the

atypical verrucous endocarditis of Libman and Sacks it is almost constant.

Cultures from the nose and throat or suspected focus of infection were made in 62 cases. The results are shown in Table 3. Although these cultures were made in the routine laboratory, and it is quite possible that a higher incidence of hemolytic streptococci might have been found by special techniques, this organism was the predominant one in at least 44% of the cases. This is only about half its incidence in Longcope's cases. Rake[26] gives an even higher percentage, stating that "99 per cent of cases of nephritis follow a streptococcal infection." In each of the cases of acute nephritis in this series associated with dermatitis, hemolytic streptococci were recovered from the skin lesions, in 2 in pure culture. Goodwin[11] has commented that impetigo contagiosa is often the only discoverable infection preceding nephritis in children.

TABLE 3.—ORGANISMS RECOVERED IN CULTURES FROM THROAT, SINUS, OR SKIN.

Organism.	No. of cases.
Streptococcus hemolyticus	27
Streptococcus viridans	9
Streptococci hemolyticus and *viridans*	7
Streptococci, unclassified	4
Pneumococci, Type I, II, XIV	5
Pneumococci, untyped	5
Staphylococci only	5

The interval between the onset of the preceding infection and the first symptoms of nephritis is difficult to determine with any accuracy. Many patients were admitted with well developed symptoms; indeed, often when symptoms were already subsiding, and were unable to tell when these had first appeared. A still greater number were unable to give exact dates for the preceding cold or sore throat. From the data on the records the interval was less than 1 week in 5, from 1 to 2 weeks in 29, from 2 to 3 weeks in 18, 4 weeks in 9, and 5 weeks in 3 cases. In 9 instances no record of the interval was made and in 4 it was so vague as to be meaningless.

The cardinal symptoms of acute nephritis are hematuria, edema, and hypertension. Yet as Murphy and Rastetter[25] pointed out, if the presence of all three is required for a diagnosis many mild cases will be overlooked, and not until years later when chronic nephritis is obvious will the significance of the mild early episode be apparent. The incidence of the more common symptoms are given in Table 4.

The urinary syndrome is the most important, because it is not only the most constant but is usually essential for the diagnosis. In 1 case anuric from admission to death the diagnosis was apparent from history, edema, hypertension, and nitrogen retention, and was confirmed at autopsy. In 1 other patient the initial urine was recorded as showing many red cells, but no albumin; subsequent specimens contained both. In all the other cases the urine contained

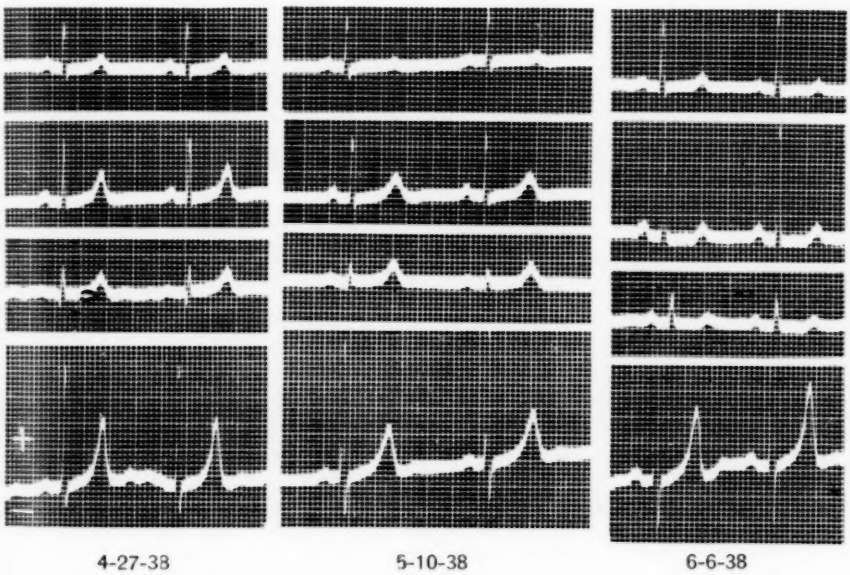

FIG. 1.—Electrocardiographic changes during the course of acute nephritis. On admission, April 27, 1938, T waves tall and peaked in Leads 2, 3, and 4R; Q–T prolonged. May 10, 1938: T^1 smaller in amplitude; T less peaked in Leads 2, 3, and 4R; Q–T prolonged. June 6, 1938: Normal record; Q–T prolonged.

both albumin and an abnormal number of red cells. Albuminuria alone is indicative of a renal lesion, but is not sufficient to justify a diagnosis of nephritis. The so-called febrile albuminuria occurs at the height of fever or infection and disappears as the temperature reaches normal. It is probably not due so much to the fever *per se* as to a temporary increase in glomerular permeability brought about by circulating toxic substances, for a similar albuminuria occurs in various afebrile toxemias and chemical poisonings. In the 20 cases in which it was recorded in this series the amount of protein varied from less than 1 gm. to 14 gm. a day; in 10 (one-half) it was less than 2 gm. Frequently there were wide fluctuations in the amount of albumin excreted from day to day. The amount of proteinuria did not bear any relation to the severity of the attack nor to the outcome. Bell[4] has shown that the amount of albumin need not correspond to the degree of glomerular damage, for those glomeruli most severely affected have closed capillaries and hence do not transmit albumin.

TABLE 4.—SYMPTOMS IN 77 CASES OF ACUTE NEPHRITIS.

Hematuria	76*
Albuminuria	75*
Casts	61
Hypertension—Systolic above 140	54
Diastolic above 90	49
Edema—Face	45
Legs	30
Pulmonary râles	18
Pleural effusion	7
Ascites	6
Nitrogen retention	33
Uremia (BUN above 90)	7
Convulsions	3
Vomiting	3

* One patient anuric from admission to death.

The degree of hematuria also varies; 31 patients had gross hematuria, in the remainder it was apparent only on microscopic examination.

The urine volume in acute nephritis is usually said to be reduced and the specific gravity high. This is in keeping with the pathologic picture of swollen, ischemic glomeruli and relatively intact tubule cells. There is a reduced renal blood flow, diminished volume of glomerular filtrate, but efficient tubular concentrating power. However, many of these patients showed specific gravities below 1.020. This raised the question among the house staff and students whether the patient did not have an exacerbation of a chronic rather than an acute nephritis. The specific gravity was recorded in 73 cases; of the 37 in which it was below 1.020, 22 were obviously losing edema at the time of admission as evidenced by a large urine volume and loss of weight. Five others were very mild cases and had been treated by forcing fluids. The remaining 10 are of particular interest. The

24-hour urine volume ranged from 220 cc. to 800 cc., averaging 340 cc. The specific gravity in one was 1.017, in the others 1.012 to 1.014. A small volume of dilute urine betokens impairment of tubular function, and therefore more extensive renal damage than is usually present. This was borne out in these cases: of the 10, 2 died in the hospital, 4 have gone on to chronic nephritis, and only 4 have recovered from the acute nephritis.

Systolic pressures above 140 mm. Hg were present in 54 cases (70%) and in 49 (64%) the diastolic was above 90 mm. Hg. The degree of elevation of blood pressure did not bear any relation to the severity of the attack nor to the outcome. Pressures of 210/150 may drop to normal in a couple of weeks, while hypertension may be absent throughout, and yet the patient go on to the development of chronic nephritis. Persistent hypertension, however, represents an unhealed renal lesion, and a rising blood pressure, even if other signs of acute nephritis have disappeared, is an unfavorable omen.

The hypertension was attributed by Volhard[33] to arteriolar spasm. It certainly is not due to increased blood volume. Goldblatt's demonstration that renal ischemia leads to persistent hypertension, and the pathologic and physiologic evidence that renal blood flow in acute nephritis is reduced makes it seem highly probable that this mechanism is responsible for the hypertension.

Edema was noted in 45 cases (59%). It was most frequently noted in the face, next about the ankles. Pulmonary râles, unassociated with obvious pulmonary infection, were recorded in 18 patients (23%). Pleural effusion was present in 7, and demonstrable ascites in 6. It must be pointed out that the criteria for edema on physical examination are very crude, and that a patient may have considerable edema before this impresses the examiner. Thirty-seven patients were weighed on admission and at frequent intervals; 6 of these lost from 1.5 kg. to 7.5 kg., average 3.7 kg. with the onset of diuresis, and yet no edema had been recognized. In those in whom edema had been recorded the loss in weight was from 0.3 kg. to 16.0 kg., average 7.1 kg.

As long ago as 1879 Goodhart[10] called attention to the occurrence of cardiac failure in the early stages of acute nephritis. At first regarded as a rarity, the incidence of demonstrable cardiac involvement has risen with the more careful studies in recent years. Whitehall, Longcope, and Williams[34] found some degree of cardiac failure as shown by dilatation of the ventricles in 17% of mild cases of acute nephritis and in 89.8% of severe cases. In the severer cases there is dyspnea, orthopnea, elevated venous pressure, and the condition may readily be mistaken for acute heart failure. In addition, many cases show alterations in the electrocardiogram, most readily detected in serial records. The cause of these evidences of cardiac involvement is not entirely clear. Alwens and Moog[2] suggested that the increased size of the heart in teleoroentgenograms was due to

pericardial effusion. But the persistence of the enlargement after edema has disappeared and arterial and venous pressure have returned to normal makes this unlikely. That the hypertension is not the sole cause is indicated by the lack of correlation between blood pressure and cardiac enlargement, and its occurrence in the absence of significant hypertension (Levy[15]) or even of any hypertension at all. Rubin and Rapoport[28] believe that there is myocardial damage from infection, and Whitehall, Longcope and Williams believe the cardiac damage is intimately associated with the pathogenesis of acute nephritis, and an expression of the widespread capillary damage which occurs. The perivascular lesions and the acute arteriolitis reported by Stone,[32] and Feller and Hurevitz[7] in biopsies from the deltoid muscle and at autopsy in 2 cases of acute nephritis support this conception. Moreover, the electrocardiographic changes reported by Levy,[15] Master, Jaffee, and Dack,[24] Langendorf and Pick,[13] and others are indicative of myocardial damage rather than mechanical factors or pericardial effusion. These consist in abnormalities of the *T* wave, low amplitude, and prolongation of auriculoventricular conduction.

Only 9 patients in this series had repeated teleoroentgenograms. Of these 5 (56%) showed a significant decrease in cardiac diameter with recovery. Electrocardiograms were made on 27 patients; of these 12 (44%) were regarded as normal records, while 15 (56%) showed some abnormalities.* Of the 12 patients showing normal tracings, 11 had only 1 record. In the 15 patients showing abnormalities, a single tracing was made in 8 instances, and two or more in 7. In the latter group, abnormalities were at times present in only one record. The abnormalities in the records consisted in alterations in the *T* wave, changes in amplitude of *QRS*, prolonged *P–R* interval, and changes in the *P* wave. These are detailed in Table 5. Thus, about half of the cases in which suitable studies were made showed evidence of myocardial damage.

TABLE 5.—ELECTROCARDIOGRAPHIC FINDINGS IN 27 CASES OF ACUTE NEPHRITIS

Normal record	13	*T* tall and peaked in I	6
Small *P* wave	3	II	8
P–R of 0.2 sec. or more	3	III	3
P–R segment depressed	1	IV	3
Abnormal left axis deviation	1	*T* negative in I	1
QRS voltage decreased	6	II	2
S–T segment elevated	1	III	1
depressed	1	*T* of Pardee type in I	3
T diphasic in II	1	II	3
IV	2	III	1
		IV	2

Thirty-three patients showed some nitrogen retention, taking 20 mg. per 100 cc. of urea nitrogen as the upper limit of normal. In the majority, however, the degree of retention was slight, 20 to

* We are indebted to Dr. Harold Feil for interpreting these records.

40 mg. per 100 cc. of blood. Seven, however, had definite uremia with blood urea nitrogen above 90; of these, 4 died. Of the other 3, 2 were in the group mentioned above who passed only a small volume of dilute urine.

Convulsions occurred in only 4 cases. Two of these were in the uremic group with one death. In the other 2, the blood urea nitrogen was 31 and 40 mg. per 100 cc. One of these died immediately after a violent convulsion; the other, in whom the spasms were very mild, recovered. Nausea and vomiting were infrequent, in only 3 severe enough to be troublesome. Six patients complained of severe headache.

Of the 77 patients, 10 died in the hospital; of these 3 deaths were apparently due to the primary disease, leaving 7 (9%) attributable to acute nephritis. Of these 4 died in uremia with marked nitrogen retention, 1 of acute cardiac failure with pulmonary edema, 1 immediately after a generalized convulsion, and 1 eight hours after admission of uncertain cause. The diagnoses were confirmed at autopsy in 9.

TABLE 6.—PROGNOSIS IN ACUTE NEPHRITIS.

	No. of cases.	Died of acute nephritis.		Followed, No.	Interval, yrs.	Cured, %.	Latent, %.	Chronic, %.	Died of nephritis, %.
		No.	%.						
Murphy and Rastetter[25]	150	12	8.0	127	2–14	58.3	..	41.7	
McPhee and Kaye[23]	90	5	5.6	48	4–7	85.4	..	14.6	
Richter[27]	100	5	5.0	77	Av. 8	80.5	..	15.5	4.0
Longcope[20b]	141	7	5.0	134	½–14	42.5	32.0	11.2	14.2
Falkers[6]	68	6	8.8	41	?	56.0	..	19.6	24.4
Leavell *et al.*[14]	82	?	..	26	1–10	77.0	19.2	3.8	
Hayman and Martin	77	7	9.1	52	½–10	67.3	17.3	9.6	5.8

Of the 67 who left the hospital, 12 were apparently cured at that time, with no edema, normal blood pressure, and normal urine. Seven of this group have been followed and all remained well. Fifty-two patients have been followed for from 6 months to 8 years, average 2.4 years. The status is shown in Table 6. Those are recorded as well who are free from symptoms, have a normal blood pressure, no albumin or red cells in the urine according to clinical methods. In 11 urea clearance tests were normal (75% or above) and in 19 specific gravities (20°/4°) of 1.020 or more gave added evidence of normal renal function. Some in the latent group, who have but recently had the acute attack will undoubtedly eventually recover. In this group are included those who have no symptoms and a normal urine, but a persistent systolic blood pressure above 140 mm. Hg (4 cases), and those who with a normal blood pressure continue to show albumin (5 cases), or albumin and red cells in their

urine. Those who have both elevated blood pressure and abnormal urine have been classed as chronic nephritis. The distribution agrees with that in other series which are shown for comparison.

All of the patients in this series who are classed as cured have shown a normal urine and blood pressure within 1 year after the acute attack, the majority within 6 months. Addis says healing occurs in the first year in 75% of those who recover and that there is no record of healing after 5 years. Since there is so little that can be done for the patient with chronic nephritis, this emphasizes the need for every effort to promote healing in the acute attack. What is the outlook for the patient who has recovered from acute glomerulonephritis? Is he more resistant or more susceptible? Although it is generally accepted that once healed acute nephritis does not recur, there is little in the literature to support this impression. Longcope reported 4 cases out of a series of 24 healed acute nephritis who subsequently showed hemolytic streptococci in one or more throat cultures without urinary abnormalities, and Loeb *et al.*[17] have recently described 10 patients who had been observed through an initial attack of acute nephritis, through a healed period, and through a subsequent infection with hemolytic streptococci without developing another bout of acute nephritis. On the other hand, Boyle *et al.*[5] reported 2 children who had had two distinct attacks of nephritis, each followed by complete recovery, and Richter[27] mentions one. We have as yet not seen a patient with two clear cut attacks of acute glomerulonephritis.

Summary. Of 77 cases of acute glomerular nephritis, 75% followed infection of the upper respiratory tract. While the disease occurs at all ages, it is most common before 30. The cardinal symptoms of hematuria, hypertension, and edema were not all present in every case. Evidence of cardiac involvement was present in approximately half the cases subjected to adequate study. Ten patients died in the hospital, 7 (9%) primarily of acute nephritis. Fifty-two of the remaining 67 patients were followed for 6 months to 8 years. Of these 35 (67.3%) are well, 9 (17.3%) have persistent albuminuria or hypertension, while 3 have died in uremia since discharge from the hospital, and 5 have chronic glomerular nephritis.

REFERENCES.

(1.) **Addis, T. H.**: Bull. Johns Hopkins Hosp., **49**, 203, 1931. (2.) **Alwens, W.**, and **Moog, O.**: Deutsch. Arch. f. klin. Med., **133**, 364, 1920. (3.) **Baehr, G.**, and **Schifrin, A.**: Libman Ann., **1**, 125, 1932. (4.) **Bell, E. T.**: Am. J. Path., **12**, 801, 1936. (5.) **Boyle, H. H., Aldrich, C. A., Frank, A.**, and **Borowsky, A.**: J. Am. Med. Assn., **108**, 1496, 1937. (6.) **Falkers, L. M.**: J. Iowa Med. Soc., **25**, 552, 1935. (7.) **Feller, A. E.**, and **Hurevitz, H. M.**: Am. Heart J., **16**, 568, 1938. (8.) **Goldring, W.**: Med. Clin. North America, **14**, 1551, 1931. (9.) **Goldring, W.**, and **Wyckoff, J.**: J. Clin. Invest., **10**, 355, 1931. (10.) **Goodhart, J. F.**: Guy's Hosp. Rep., **24**, 158, 1879. (11.) **Goodwin, T. C.**: Med. Clin. North America, **21**, 1379, 1937. (12.) **Kayser-Petersen, J. E.**, and **Schwab, E.**: München. med. Wchnschr., **69**, 580, 1922. (13.) **Langendorf, R.**, and **Pick, A.**: Acta med. Scand., **94**, 1, 1938. (14.) **Leavell, B. C., Becksmith, J. R.**, and **Wood, J. E., Jr.**: Virginia Med. Month., **66**,

226, 1939. (15.) **Levy, I. J.**: Am. Heart J., **5**, 277, 1930. (16.) **Lichtwitz, L.**: Praxis d. Nierenkrankheiten, 2d ed., Berlin, Julius Springer, 1925. (17.) **Loeb, E. N., Lyttle, J. D., Seegal, D.,** and **Jost, E. L.**: J. Clin. Invest., **17**, 623, 1938. (18.) **Loeb, R. F.**: Med. Clin. North America, **14**, 1545, 1931. (19.) **Löhlein, M.**: Ueber die entzündlichen Veränderungen der Glomeruli der menschlichen Nieren und ihre Bedeutung für die nephritis, Leipzig, S. Hirzel, 1907. (20.) **Longcope, W. T.**: (*a*) Bull. Johns Hopkins Hosp., **45**, 335, 1929; (*b*) Internat. Clin., **1**, 1, 1938. (21.) **Lucchesi, P. F.,** and **Bowman, J. E.**: J. Am. Med. Assn., **103**, 1049, 1934. (22.) **McCrae, J.**: Trans. Assn. Am. Phys., **28**, 194, 1913. (23.) **McPhee, I. M.,** and **Kaye, G.**: Med. J. Australia, **2**, 14, 1932. (24.) **Master, A. M., Jaffe, N. L.,** and **Dack, S.**: Arch. Int. Med., **60**, 1016, 1937. (25.) **Murphy, F. D.,** and **Rastetter, J. W.**: J. Am. Med. Assn., **111**, 668, 1938. (26.) **Rake, G. W.**: Guy's Hosp. Gaz., **42**, 263, 1928. (27.) **Richter, A. B.**: Ann. Int. Med., **9**, 1057, 1936. (28.) **Rubin, M. I.,** and **Rapoport, M.**: Penna. Med. J., **40**, 1029, 1937. (29.) **Salvesen, H. A.**: Acta med. Scand., **96**, 304, 1938. (30.) **Seegal, D.**: Arch. Int. Med., **56**, 912, 1935. (31.) **Seegal, D., Seegal, B. C.,** and **Lyttle, J. D.**: J. Am. Med. Assn., **105**, 17, 1935. (32.) **Stone, W. J.**: Bright's Disease and Arterial Hypertension, Philadelphia, W. B. Saunders Company, 1936. (33.) **Volhard, F.**: *In* Bergman and Staehelin Handb. d. inn. Med., Berlin, Julius Springer, vol. **6**, Part II, 1931. (34.) **Whitehall, M. R., Longcope, W. T.,** and **Williams, R.**: Bull. Johns Hopkins Hosp., **64**, 83, 1939.

THE MOTOR REACTION OF THE DOG'S COLON TO INTRAVENOUS INJECTIONS OF E. COLI COMMUNIOR, SPIRILLUM RUBRUM AND STAPHYLOCOCCUS AUREUS.

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The toxic effects of dead colon bacilli or fractions thereof have been discussed by various investigators. Such effects are mainly referable to the gastro-intestinal,[1] pulmonary[3,8] cardiovascular,[3] and central nervous systems[7]; and to temperature regulation.[8] Ecker and Biskind[1] in a series of observations on laparotomized dogs with the spinal columns crushed in the lower thoracic region reported no visible effects from intravenous injections of filtrates of *E. coli communior* on intestinal movements. On the other hand diarrhea, vomiting and tenesmus have been reported to follow intravenous injections of the dead bodies of this organism.[7] The work of Vaughan[8] and of Wheeler[9] indicates that the toxic substance associated with *E. coli communior* is intracellular and therefore would not be expected to be found in such filtrates as those used by Ecker and Biskind. The rapidity with which the toxic substance becomes active following intravenous injection of the whole dead organism is shown by the work of Templeton, Ferguson and Pilot,[7]

who reported gastro-intestinal upsets within 10 minutes, and a general depression within 1½ hours.

In a preliminary report Galapeaux, Adler, Ferguson and Templeton[2] called attention to a marked depression in colon activity, retching, vomiting and defecation resulting from intravenous injections of colon bacillus vaccines. They also pointed out that the activity of the colon was increased immediately prior to a defecation. This work has been subsequently extended to include studies on 5 dogs.

The animals used were cecostomized several weeks prior to this study and were trained to lie quietly on a cushioned table in the presence of ordinary noises and other disturbances encountered in the laboratory. The motility of the colon was recorded by two tandem balloon[4] systems as previously described.[5,6] Each tandem system consisted of three balloons, 3 cm. in diameter and 3 cm. in length, arranged in linear order and separated from each other by a distance of 3 cm. One system of balloons was inserted by way of the cecostomy for recording proximal colon motility and one system inserted through the anus to record distal motility. Each balloon was connected to a water manometer by way of a T tube. After the insertion of the systems, the balloons were alternately inflated and deflated a number of times to smooth out their contours, after which 6 cm. of water pressure was drawn against them for the purpose of standard deflation. Eight centimeters of water pressure was raised in each manometer and continuity between them and the deflated balloons was then established. By this method simultaneous records were obtained from six segments of the colon.

The colon bacillus vaccine used in this study was prepared from a stock culture kept on artificial media in the Loyola laboratories for the past 8 years. Nutrient agar was used as the medium on which the organisms for the vaccines were grown. After 48 hours of growth in coli flasks the organisms were washed with tap water into bottles and sterilized at a temperature of 56° C. for 30 minutes. Tests for sterility were made by plating on nutrient agar. The stock vaccines made from these cultures contained 6 to 9 million organisms per c.mm. Dilutions for injections were made at the time of use.

Before injections of the vaccines were begun, 21 control experiments of 400 minutes' duration were made on the animals used, in which no injections or interruptions occurred in the course of the experiment. The tracings thus obtained were then divided into 8 periods of 50 minutes each. The quantity of activity was calculated by considering only the time during which the gut was active. To accomplish this, two rules were rigidly followed. First, a segment of the colon was considered active if a contraction or contractions lasted for 1 or more minutes; and second, a period of quiet was considered to exist if no activity appeared in a segment for 2 minutes. The quantity of motility thus calculated in terms of percentage revealed an average activity varying between 59 to 66%.

The average activity recorded in each of the last four periods of the control tracings showed an approximate equal tendency to be above or below the average activity per 50 minutes of the first 200 minutes of the experiment.

Tracings of the same duration and under the same conditions were obtained from the animals used in the control study in which after a 200-minute control period 1 cc. of a diluted vaccine was injected intravenously. The vaccine injected was prepared from the stock solution previously described by diluting with sterile tap water in 1 to 7 proportion. From a series of 46 experiments, each having a control period of 200 minutes, following which the vaccine was injected, and 20 experiments in which no vaccine was injected, a

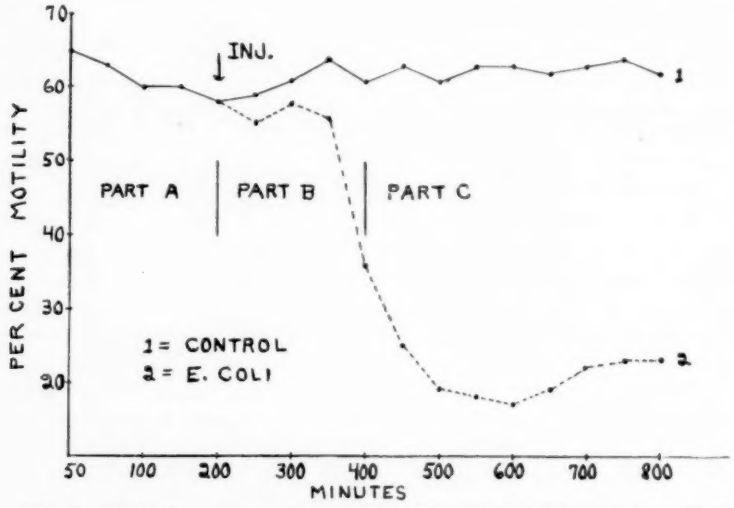

FIG. 1.—Ordinate — per cent of colon motility calculated in minutes. Abscissa — duration of experiment. Unbroken line —— control motility. Broken line - - - - - motility after vaccine injection.

total of 66 experiments were obtained, each having a 200-minute control period (see Fig. 1, Part A). The activity of this control period varied from 56 to 64% the higher activity being in the first part of the experiments. During the second 200 minutes (Fig. 1, Part B), the control activity based upon 20 experiments during which no injections were made, varied from 59 to 64%. In those experiments in which the vaccines were injected at the close of a 200-minute control period, the activity was decreased below that of the controls throughout the succeeding periods of study. The activity of the first 50 minutes following the injection was somewhat depressed. This depression in turn was followed during the next 50 minutes by a slight rise in activity, although the percentage did not reach that of the control experiments. The duration of these

experiments, although adequate to show a marked depression in the last 50-minute period (between 150 and 200 minutes after the injection) was not sufficiently long to reveal the duration of this depression.

By another method of tabulation the relation of the quantity of activity of each 50-minute period following the injection was compared to the average quantity of activity of the four 50-minute periods preceding the injection. This method of compilation revealed that out of 46 experiments, only 26% showed activity in the first 50 minutes after injection to be above the average activity of the 200 minutes preceding the injection, thus supporting the compilation previously made which suggested a depression in colon activity during the first 50 minutes following the injection. In the succeeding two 50-minute periods, the opportunities for the activity to be above or below that of the average in the control periods seemed to be about equal; 56 and 52% of the experiments in the second and third periods respectively revealed activity above that of the average in the control periods. The most significant change in activity (Fig. 1) was seen between 150 and 200 minutes after the injection. This was marked by a depression in activity from approximately 56 to 35%. It is also significant that 81% of the experiments revealed a depression at this time.

Since no evidence of a return to normal activity was seen in the experiments of 400 minutes' duration, the necessity for longer experiments was obvious. For controls, 10 records were continued for an additional 400 minutes. In parallel, 19 experiments each with a 200-minute control period were followed for 600 minutes after the injection. The most significant depression of activity which occurred between 150 and 200 minutes, as previously described, was found to continue for approximately 4 hours. A slow return towards the normal was usually evident before the close of the experiment, and a complete return of normal activity was established within 16 hours at which time further control tracings were obtained. During the last 400 minutes 95 to 100% of all the experiments (Fig. 1) revealed a decrease in activity below that of the average activity in the control periods.

During the course of an experiment the reactions of the animals were carefully observed. About 30 minutes after the injection, an increase in salivation and some restlessness was commonly seen. Thirty to 40 minutes later, vomiting or defecation, or both, was frequent. These latter reactions continued at intervals for several hours. Just prior to a defecation there was an increase in the quantity of activity involving the colon as a whole. Following defecation there was usually a decrease in the quantity of activity.

Although the balloon method of recording is designed primarily for recording circular activity, in a few instances we observed a shortening of the colon to such an extent that longitudinal activity

must have made some impression on the balloons. In 4 instances during the period of defecation the distal balloon set was expelled and the distal balloon of the proximal set was also expelled through the anus. Since the proximal set was not free to move, being anchored at its entrance into the gut, the extrusion of its distal balloon through the anus must have been accomplished by a marked shortening of the longitudinal musculature. This mechanism may be of great importance in transporting fluid material of the proximal segments into the distal colon and may account in part for the further observation that at the termination of experiments the defecation which followed were of diarrheal consistency.

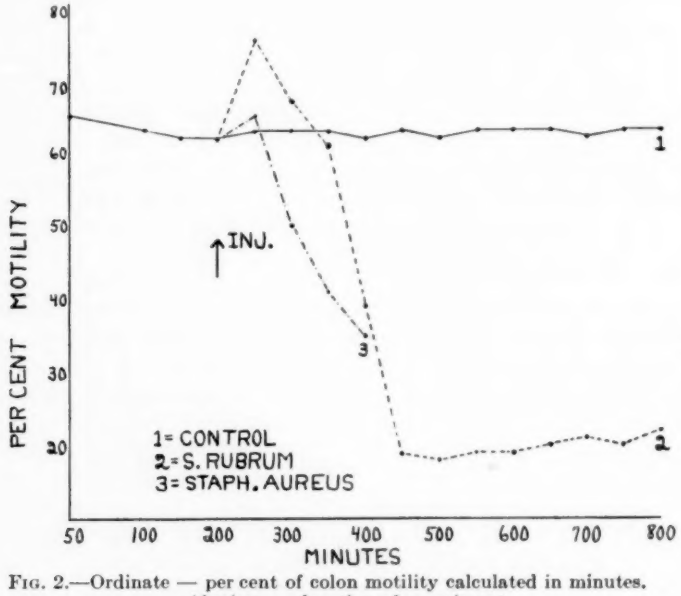

FIG. 2.—Ordinate — per cent of colon motility calculated in minutes. Abscissa — duration of experiment.

At times following an injection of *E. coli* vaccine, the animals ejected fluid material through the anus by violent contractions of the abdominal muscles, unassociated with activity of the colon which was recordable by the technique used in this study. The urinations observed in this study were usually initiated by vigorous abdominal contractions. In view of the profound reaction elicited by the dead bodies of *E. coli communior* on colon activity when injected intravenously, this study was extended to include two other organisms, *Spirillum rubrum* and *Staph. aureus*, which ordinarily exhibit a low toxicity. The vaccines of these organisms were prepared in the same manner as that of *E. coli communior*. Two of the

same animals were used and the same technique employed as previously described in this article.

In this study of the effects of intravenous injections of *S. rubrum* and *Staph. aureus* vaccines on colon motility, 52 experiments were conducted. In all cases the first 200 minutes were considered as a control period in which no experimental variations were introduced. At the close of this period intravenous injections of 4 cc. of a stock vaccine of *S. rubrum* containing 12 million organisms per c.mm. were given in 28 experiments, 20 of which were terminated at the close of 200 minutes and 8 continued for 600 minutes after the injection. In 11 experiments 4 cc. of a stock vaccine of *Staph. aureus* containing 12,200,000 organisms per c.mm. were given intravenously at the close of the 200-minute control period and continued for 200 minutes. Thirteen of the experiments were continued for 800 minutes without experimental intervention for controls. During the 200-minute control period the average number of the minutes of activity in 52 charts (Fig. 2) was found to vary from 65 to 68%. The average activity in the control experiments for the next 600 minutes varied from 64 to 70%. The most significant effect relative to motility was a decrease in the activity about 100 to 150 minutes after the injections, which was observed in the case of *S. rubrum* to become more profound during the next 200 minutes and to last for several hours.

All studies on *Staph. aureus* were terminated 200 minutes after the injection; however, the depression had reached a very significant level before the close of the experiments.

Although the number of organisms per c.mm. injected was much greater than that used in the study of *E. coli communior*, the general reaction of the animal was much the same. Nausea as indicated by increased salivation and movements of the jaws, vomiting and defecation were common occurrences.

Summary. 1. A slight depression in colon activity was observed during the first 50 minutes following the intravenous injection of *E. coli communior*.

2. The average activity per 50-minute period was somewhat increased between 50 and 150 minutes after an intravenous injection of *E. coli vaccine*.

3. Between 150 and 200 minutes after an intravenous injection of *E. coli* vaccine a profound depression began which persisted for several hours following which there was a slow return to normal.

4. Twenty-four hours after an intravenous injection of *E. coli* vaccine the quantity of colon activity had returned to normal.

5. An increase in the quantity of colon activity was observed immediately preceding the act of defecation elicited by an intravenous injection of *E. coli*.

6. Following the intravenous injection of *E. coli* vaccine all animals displayed signs of a general reaction to the vaccine such as

salivation, restlessness, periodic increased respiration and heart rate, abdominal distress indicated by a periodic hypertonicity of the abdominal muscles, vomiting, defecation and occasionally urination.

7. Occasionally, following the intravenous injection of *E. coli* vaccine, fluid material was expelled from the colon at the time of violent contractions of the abdominal muscles unassociated with a demonstrable colon activity.

8. The most significant result following intravenous injection of *S. rubrum* and *Staph. aureus* was a depression of colon motility becoming profound 150 to 200 minutes after injection.

The authors are indebted to Dr. A. J. Carlson, who made this study possible.

REFERENCES.

(1.) **Ecker, E. E.**, and **Biskind, M. S.**: Arch. Path., **7**, 204, 1929. (2.) **Galapeaux, E. A., Adler, H. F., Ferguson, R. L.**, and **Templeton, R. D.**: Am. J. Physiol., **123**, 72, 1938. (3.) **Koessler, K. K., Lewis, J. H.**, and **Walker, J. A.**: Arch. Int. Med., **39**, 188, 1927. (4.) **Templeton, R. D.**, and **Bollens, W. F.**: J. Lab. and Clin. Med., **15**, 585, 1930. (5.) **Templeton, R. D.**, and **Lawson, H.**: Am. J. Physiol., **96**, 667, 1931; J. Lab. and Clin. Med., **17**, 1244, 1932. (6.) **Templeton, R. D., Bollens, W. F., Lawson, H., Lutz, A., Borkon, E. L.**, and **Galapeaux, E. A.**: Am. J. Physiol., **116**, 153, 1936. (7.) **Templeton, R. D., Ferguson, R. L.**, and **Pilot, I.**: Unpublished data. (8.) **Vaughan, V. E.**: J. Am. Med. Assn., **44**, 1340, 1905. (9.) **Wheeler, S. M.**: J. Am. Med. Assn., **44**, 1271, 1905.

AN EVALUATION OF THE BRUCELLA OPSONOCYTOPHAGIC TEST.

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Among the laboratory procedures employed as diagnostic aids in suspected cases of brucellosis, the opsonocytophagic test has been used extensively. It is the purpose of this paper to examine the limitations and usefulness of this test. The data reported here have been accumulated from studies carried out on hospital patients, medical students, and members of the staff of Duke Hospital.

Method. The technique of the opsonocytophagic test as outlined by Huddleson[4] has been followed. A laboratory strain of *Brucella melitensis* var. *suis* obtained from Huddleson and an encapsulated strain of *Brucella melitensis* var. *suis*, isolated from a patient having Hodgkin's disease, have been used for the bacterial suspensions. The latter strain was used because this strain and others, isolated from patients having Hodgkin's disease, have been found to differ significantly from the laboratory strains.[6] The bacterial suspensions have been standardized by means of the photronreflectometer to a density of 3 billion organisms per cc. Whenever intradermal tests with Brucellergin were made, the determination of the opsonocytophagic index and the agglutinin titer of the patient's serum has always been carried out before the skin test. The opsonocytophagic index number has been calculated by the method of Foshay and Le Blanc.[3]

Normal Range of the Brucella Opsonocytophagic Index. We have scrutinized our data very closely to determine the usual range of phagocytosis of *Brucella* organisms by the neutrophils of normal individuals, and have carried out simultaneous determinations of the opsonocytophagic index for *Eberthella typhosa*, *Salmonella suipestifer*, and *Proteus vulgaris*, using the same technique, in order to determine the usual range of phagocytosis of these organisms. The following table gives the range of the great majority of opsonocytophagic indices in normal individuals.

TABLE 1.—RANGE OF THE BRUCELLA OPSONOCYTOPHAGIC INDEX AND INDEX NUMBER IN NORMAL INDIVIDUALS.

	No. of bacteria ingested per neutrophils.				Opsonocytophagic index number.
	0.	1–20.	21–40.	41+.	
Lowest limit of normal range . .	25	0	0	0	0
Usual upper limit of normal range .	0	25	0	0	25

In any series, however, a few indices will be found such as 3-20-2-0. Because these minor variations in the index are not infrequent, we consider an index number of 30 to represent the upper limit of normal phagocytosis, and within this range falls the phagocytosis of the three organisms studied for purposes of comparison with *Brucella*. We do not distinguish between "negative" and "weak" phagocytosis as does Evans,[1] although her range for those, from an index number of 1 to 20 and from 21 to 30 respectively, corresponds with our range of normal or "negative" phagocytosis.

Specificity of the Brucella Opsonocytophagic Index. The question of the specificity of the *Brucella* opsonocytophagic index was raised early in this study. To determine whether the neutrophils of individuals phagocytosing *Brucella* organisms in high degree would phagocyte other organisms, simultaneous tests were made with a given blood sample using equivalent suspensions of *Eberthella typhosa*, *Salmonella suipestifer*, and *Proteus vulgaris*. The individuals used for this purpose were patients proven to be suffering from *Brucella* infection by the isolation of the organism, and healthy individuals having high degrees of phagocytosis for *Brucella* organisms. The results of this study are presented in Table 2, and show that in no instance was there significant phagocytosis of any of the other three organisms.

TABLE 2.—SPECIFICITY OF THE BRUCELLA OPSONOCYTOPHAGIC TEST.

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
	Opsonocytophagic Index Numbers																						
Brucella melitensis var. *suis* (non-encapsulated)	81	52	90	89	56	45	47	63	39	0	39	41	40	81	60	45	69	48	36	47	67	94	59
Brucella melitensis var. *suis* (encapsulated)	.	.	.	.	.	.	.	.	.	39	37	5	27	70	23	39	29	2	10	15	7	35	50
Eberthella typhosa . . .	18	5	12	0	6	19	15	23	29	0	0	10	27	20	20	24	2	4	20	22	3	0	17
Salmonella suipestifer . .	22	9	17	3	5	29	5	21	20	5	15	5	3	5	13	5	9	8	6	20	0	10	11
Proteus vulgaris	.	.	.	0	1	18	0	27	12	2	13	0	3	0	27	0	6	0	22	10	3	15	4

Comparison of the Opsonocytophagic Index With Different Brucella Strains. The finding that many *Brucella* organisms isolated from patients having Hodgkin's disease are encapsulated, and differ significantly from the usual laboratory strains, led to a comparison of the opsonocytophagic indices, using equivalent bacterial suspensions of a non-encapsulated laboratory strain and of an encapsulated strain. Distinct differences in the degrees of phagocytosis have been found in many instances, which indicates the desirability of carrying out such determinations with both encapsulated and non-encapsulated strains. Similar differences have been found in the agglutination reactions using the two strains. Table 3 gives the results of such opsonocytophagic index determinations in 105 individuals.

TABLE 3.—DIFFERENCES IN THE OPSONOCYTOPHAGIC INDEX WITH NON-ENCAPSULATED AND ENCAPSULATED BRUCELLA STRAINS IN 105 INDIVIDUALS.

	Opsonocytophagic Index No.				
	0–30.	31–40.	41–60.	61–80.	81–100
Non-encapsulated strain .	95	22	17	5	1
Encapsulated strain . .	95	13	6	3	0

Forty-one of the 105 individuals studied had positive *Brucella* opsonocytophagic indices. Of these, 28 indices were positive with the laboratory strain alone; 6 with the encapsulated strain alone; 7 with both strains.

Comparison of the Brucella Opsonocytophagic Test With the Agglutination and Allergic Skin Test. Close comparison of the results of intradermal tests with Brucellergin, agglutination reactions, and opsonocytophagic index determinations shows that the latter yields by far the greatest percentage of positive reactors. From the study of groups of patients suffering from a variety of diseases, and of normal individuals, the opsonocytophagic test has, apparently, a distinct usefulness in attempting to survey the incidence of contact with *Brucella* organisms in groups of individuals. The following table illustrates our findings.

TABLE 4.—SUMMARY OF LABORATORY TEST FINDINGS IN DIFFERENT GROUPS OF INDIVIDUALS.

	No. of individuals studied.	Positive Brucellergin intradermal tests, %.	Positive *Brucella* agglutinations, %.	Positive *Brucella* opsonocytophagic indices, %.
New Haven Hosp. patients†	96	6.2	55.1	72.9
Duke Univ. School of Medicine students	50	10.0	22.0	40.0
Duke Hosp. patients, Series I* . . .	196	11.1	19.3	39.2
Duke Hosp. patients, Series II* . . .	105	..	28.5	37.1

* In Series I, the *Brucella* opsonocytophagic index and agglutination reactions were determined only for a standard laboratory strain. In Series II, both this non-encapsulated laboratory strain and an encapsulated *Brucella* strain were used.

† I wish to thank Dr. F. G. Blake and Dr. A. W. Oughterson for the privilege of using the data on these patients.

Discussion. On the basis of the degree of phagocytosis of *Brucella* organisms by an individual's neutrophils, several systems of classification and interpretation of the opsonocytophagic index have been made.[1,4] Huddleson's interpretation, requiring also the allergic skin test, has attracted particular attention and the limitations and inconsistencies of this system have been pointed out by several investigators.[2,5] On the basis of our experience we think that a positive *Brucella* opsonocytophagic index indicates only that a given individual has had contact with *Brucella* organisms, and reveals nothing as to the activity of *Brucella* infection. This point of view is confirmed by the finding of positive degrees of phagocytosis in healthy individuals, with no clinical history to suggest previous *Brucella* infection, and in individuals given killed *Brucella* organisms by the subcutaneous route. A negative *Brucella* opsonocytophagocytic index does not exclude contact or infection with *Brucella* organisms. In cases of proven brucellosis, and of *Brucella* infection coëxisting with Hodgkin's disease, any significant degree of phagocytosis is frequently entirely lacking during active phases of the disease, and particularly when bacteremia is present. Similarly, opsonocytophagic indices repeated over a period of several months may show quite variable results. The effect of previous injections of Brucellergin, Brucellin, or *Brucella* vaccines upon the opsonocytophagic index, as well as upon the agglutination reaction, is well known and is mentioned only for emphasis. In no way is the opsonocytophagic test diagnostic of active *Brucella* infection.

Summary and Conclusions. 1. The usual range of the *Brucella* opsonocytophagic index in normal individuals, as expressed by the index number, is from 0 to 30.

2. A positive *Brucella* opsonocytophagic index is specific, that is, the individual's blood that is positive for *Brucella* does not phagocyte other organisms to any considerable degree.

3. A significant difference in the phagocytosis of non-encapsulated and encapsulated strains of *Brucella* organisms exists, and should be considered when this test is carried out.

4. The *Brucella* opsonocytophagic index has its greatest usefulness in indicating contact with *Brucella* organisms and, of the usual laboratory tests, is the single most useful test for survey work.

5. The *Brucella* opsonocytophagic index is not diagnostic of active *Brucella* infection and may be negative even when active infection exists.

REFERENCES.

(1.) **Evans A. C.**: Pub. Health Rep., **52**, 1419, 1937. (2.) **Foshay, L.**: Am. J. Clin. Path., **10**, 176, 1940. (3.) **Foshay, L.**, and **Le Blanc, T. J.**: J. Lab. and Clin. Med., **22**, 1297, 1937. (4.) **Huddleson, L. F.**: Brucellosis in Man and Animals, New York, The Commonwealth Fund, 1939. (5.) **Menefee, E. E., Jr.**, and **Poston, M. A.**: Am. J. Med. Sci., **197**, 646, 1939. (6.) **Mickle, W. A.**: Capsule Formation by Members of the Brucella Group, J. Infect. Dis. (in press).

INTUBATION STUDIES OF THE HUMAN SMALL INTESTINE.

XIII. THE CONCENTRATION AND MOVEMENT OF GLUCOSE SOLUTIONS IN THE STOMACH AND DUODENUM.*†

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IT is probable that when a reasonable quantity of glucose is ingested it passes down the alimentary canal in progressively diminishing amount until all of it is absorbed. The amount and rate of absorption vary from mouth to anus and depend, in part, on the concentration of the solution and on the duration of contact with the mucosa in each area. Previous studies have shown, however, that, irrespective of the solution ingested, a concentration above 5% or 6% is rarely observed in the jejunum or ileum and that when stronger solutions are placed directly in the small intestine the processes of dilution, absorption and dispersion of the fluid along the gut reduce the concentration to a low level within a very few minutes. From this dilute solution the intestine can nevertheless withdraw the glucose at a rate unexplainable by simple osmotic diffusion and in amounts proportional to the concentration.[1a]

Implied by these observations are certain points concerning the behavior of the glucose prior to its reaching the jejunum, and it is the purpose of this and the two subsequent papers to consider the changes that take place in the ingested glucose solutions while still on the proximal side of the duodeno-jejunal junction. This report deals, 1, with the question of whether or not an initial delay occurs following the taking of a hypertonic solution before it begins to traverse the duodenum; 2, with the proportion of the total amount of glucose ingested that reaches the duodeno-jejunal junction; and 3, with the gradient of concentration throughout the stomach and duodenum during the period of gastric emptying. Preliminary reports on this work have already appeared.[1a,b,5]

I. Is the onset of gastric emptying delayed when a hypertonic glucose solution is ingested?

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Method. Normal adult human subjects were carefully selected for these experiments. To determine visually the appearance time of glucose in the duodenum and jejunum after the administration of a markedly hypertonic solution, barium sulphate was added to a 50% solution and the mixture swallowed by 11 normal individuals. Each subject was instantly placed in the prone position on the fluoroscopic table and the time of passage of the barium sulphate-glucose mixture observed.

Results. Table 1 shows that in most instances the opaque mixture was visible in the duodenum within 2 minutes or less after its administration.

TABLE 1.—GASTRIC AND DUODENAL EMPTYING TIME—FLUOROSCOPIC OBSERVATIONS.
(Ingestion of 100 cc. 50% glucose plus $BaSO_4$.)

No. of cases.	Enters duodenum.	No. of cases.	Enters jejunum (min.).
4	0–10 sec.	4	1
4	10–30 sec.	4	1–5
2	1–2 min.	1	12
1	30 min.	1	34
		1	52

Ages, 20 to 28 years. Heights, 5 ft. 1 in. to 6 ft. 2 in. Weights, 112 to 165 pounds.

Discussion. The results agree with the statement of Pendergrass[9] that there is no appreciable delay in the admission of a concentrated glucose solution into the jejunum. The poor initial recoveries from the duodenum after highly concentrated test meals, as shown in Chart 1, might in the absence of the roentgenologic evidence be interpreted as indicating a delay in the onset of gastric emptying, but more probably it is due to the rapid absorption of the first ejections before dilution has greatly increased the volume.

II. What proportion of the ingested glucose reaches the jejunum?

Method. A complete collection of all the intestinal contents reaching the duodeno-jejunal junction after a test meal of glucose was made by applying constant suction to the gut lumen at that point. An obstructing balloon mounted on a second lumen of the same tube and just beyond the point of suction was kept distended in the upper jejunum. As the aspiration apparatus under working conditions has a withdrawal capacity of 150 cc. of intestinal contents per minute, we believe that no leakage past the balloon occurred. Glucose was taken by mouth or injected into the stomach through a separate tube after the withdrawal of fasting specimens. In the short experiments the stomach and duodenum were quickly emptied and washed through separate tubes. In the experiments which were carried on until practically all of the ingested glucose was absorbed the gastric and duodenal residue was withdrawn by the same tube that had been used during the experimental period for duodeno-jejunal aspiration. In either case the speed of emptying and washing was sufficiently great to give a satisfactorily clean-cut absorption time.

Considering the glucose from the duodeno-jejunal junction as that fraction of total amount ingested which would have been absorbed in the jejunum and ileum, one may then determine the ratio of gastro-duodenal to jejuno-ileal absorption.

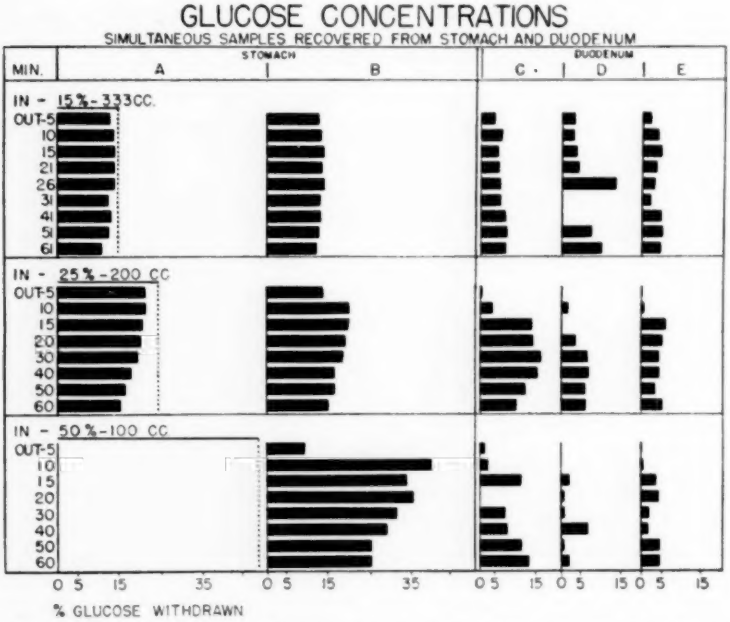

CHART 1.—The results of three experiments selected to contrast the effect on duodenal concentrations of the ingestion of widely different volumes and concentrations of glucose.

The samples were analyzed by the method of Benedict after filtrates were prepared according to Somogyi as reported in a previous paper.[6]

Results. Twenty-five experiments were performed (Table 2) in which the amounts of glucose ingested varied from 25 to 150 gm., the volume from 25 to 500 cc. and the concentrations from 5 to 50%. The duration of the experiments varied from 30 minutes to 4 hours. In 2 instances, only, was as much glucose recovered from the duodeno-jejunal junction as was absorbed in the stomach and duodenum, and in some instances essentially no glucose was obtained from this point. The amount leaving the duodenum was rather independent of the amount ingested and exceeded 9.6 gm. only in 3 instances.

Discussion. When glucose is ingested, even in large amounts, only a few grams of it reach the jejunum. This must mean an extraordinary power of absorption on the part of the duodenum or

a participation by the stomach in the absorption of glucose, particularly from highly concentrated solutions. As the first step in determining what the actual power of these portions of the digestive tube is with regard to absorption, it becomes important to know the concentrations actually occurring while absorption is normally in progress.

TABLE 2.—THE RATIO OF ABSORPTION ABOVE AND BELOW THE DUODENO-JEJUNAL JUNCTION.

Case No.	In stomach.		Absorbed above D.-J. junction.	Recovered from D.-J. junction.	Ratio.
	%	Gm.			
215	5	25	18.0	6.9	2.6
149B	20	40	11.2	0.3	37.0
145	25	50	47.4	2.6	18.0
146	25	50	30.8	19.2	1.6
151	25	75	40.7	0.0	
211	50	25	23.7	1.8	13.0
219	50	25	22.3	2.7	8.3
208	5	25	23.0	0.8	29.0
148A	15	30	17.9	5.8	3.1
149A	15	30	9.5	1.4	6.8
207	50	24	21.5	1.3	17.0
220	50	25	21.5	3.5	6.1
147A	15	30	23.4	1.3	18.0
159	25	75	20.3	7.7	2.7
156	33	100	25.6	7.3	3.5
157	20	100	19.0	1.1	17.0
150	25	75	34.2	1.2	28.0
152	25	75	12.5	2.6	4.8
155	33	100	16.9	9.6	1.8
161	25	75	18.4	7.9	2.4
162	25	75	11.9	13.0	0.9
154	33	100	87.9	2.2	40.0
163	5.4	27	12.3	6.8	1.8
160	50	150	12.9	14.4	0.9
158	25	75	26.6	0.3	
212	50	25	..	0.1	

NOTE.—The variations in the quantities absorbed are in large part due to variations in the lengths of the experiments.

III. At what concentrations may glucose be recovered from selected points in the stomach and duodenum?

Method. By the use of a 2- and of a 3-lumened tube, perforated at appropriate points and inserted at the same time, five samples of contents from predetermined areas of the stomach and duodenum were recovered at practically simultaneous time intervals after the ingestion of a hypertonic glucose solution. The points in the digestive tract which were sampled are indicated in Figure 1. The position of the tubes was confirmed by fluoroscopy every 5 minutes without moving the subject. Care was also taken to maintain him in a uniform position, to avoid his swallowing saliva and to prevent nausea and gagging. Analyses of the samples, therefore,

gave data for the determination of the gradient of glucose concentration for any given moment from the body of the stomach to the beginning of the jejunum. Attempts were made to recover the smallest analyzable amounts and with maximal rapidity so that the sample would not consist of a mixture of portions of several passing boluses.

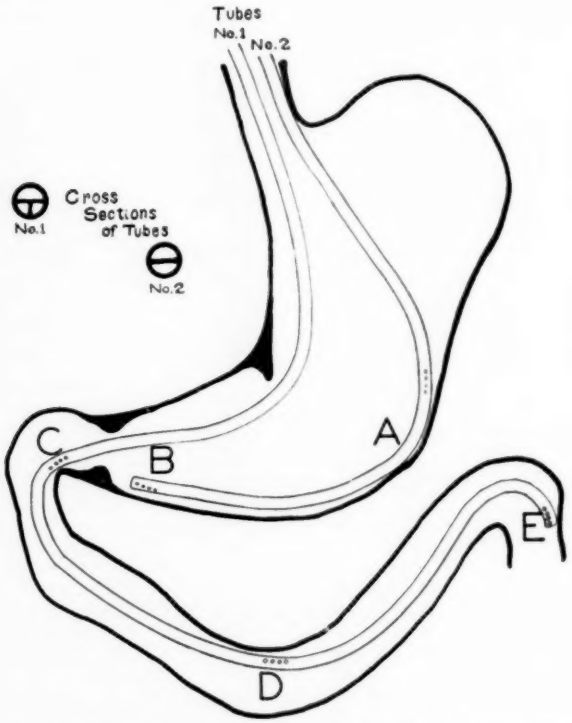

FIG. 1.—*Arrangements of two- and three-lumen tubes in the stomach and duodenum. A, B, C, D* and *E* indicate the sites from which samples were simultaneously removed at stated intervals after the ingestion of glucose solutions.

Results. Ten satisfactory experiments were performed. The data on 3 typical cases are shown in Chart 1. The fasting samples contained no glucose. Changing the concentration of the ingested solution made relatively little difference in the concentration of any of the subsequently removed duodenal specimens. From the ligament of Treitz area (*E*, Fig. 1) no specimen with a concentration over 6% was withdrawn, irrespective of the strength of the solution administered. So long as solutions of effective concentration were present in the stomach those recoverable from position *E* contained 2% to 6% of sugar. At the mid-duodenum the contents had a higher concentration, but characteristically they showed consider-

able variability. In some instances a rise from 4% to 13.4% occurred within 5 minutes in consecutive samples. A greater fall in the concentration occurred between the duodenal cap (*C*) and the mid-duodenum (*D*). This was to be expected, since the most irritable part of the intestinal tract lies between these two points. Reviewing the samples from all parts of the duodenum for the highest concentration recovered, however, it is interesting to note that, irrespective of the concentration of the specimens ingested, none containing more than 15% of glucose was ever recovered (Table 3), and that whenever a highly concentrated specimen was obtained, its volume was small.

TABLE 3.—HIGHEST CONCENTRATIONS FOUND IN DUODENUM AFTER INTRODUCTION OF HYPERTONIC GLUCOSE SOLUTIONS INTO STOMACH.

Exp. No.	Introduced.		Time of sampling (min.).	Concentration withdrawn.			
	%.	Vol. (cc.).		Pylorus (B) (%).	Duodenal cap (C) (%).	Mid-duodenum (D) (%).	Treitz ligament (E) (%)
142 . . .	25	200	36	18.0	7.5	**12.4**	
174 . . .	15	333	21	13.5	4.3	4.2	3.5
174 . . .	15	333	26	12.9	4.8	**13.4**	2.9
173 . . .	25	200	15	20.4	**12.6**	..	**6.0**
173 . . .	25	200	30	18.8	**14.9**	6.6	4.2
172 . . .	50	100	50	26.4	**10.4**	0.5	4.5

From the stomach specimens of far higher concentration were recovered, but these, for reasons to be discussed, are not strictly comparable to those from the duodenum. The rate of fall with time in the concentration of the total mixed gastric contents is given for 1 subject in Chart 2. The duration of the interval in which the concentration of the gastric contents exceeded the highest concentration for the duodenal contents in this instance was 52 minutes. The determination of this point may prove of real importance as indicating the duration of what are probably optimal conditions for duodenal absorption.

Discussion. The most important point determined by these experiments has been the maximal concentration of glucose that can leave the stomach. This figure is better obtained by observing the maximal concentration appearing in the duodenum, rather than the lowest concentration collectable from the stomach, as must become apparent on considering the differences in shape and activity of these two organs. The duodenum receives a bolus of gastric content and holds it for a brief period isolated from the material remaining in the stomach. During this interval the lively activity of its walls, the movement of the villæ, and the high ratio of mucosal surface to contained solution all facilitate the rapid dilution and absorption of the glucose contained.

In the stomach, on the other hand, the conical shape and active peristalsis of the antrum, in free communication as it must be with the capacious and inactive fundus, results in a very different rela-

tionship between the viscus and its contents. The deep peristalsis of the antrum results in so much better mixing of its contents than occurs in the fundus that the concentration of specimens from just proximal to the pylorus may be higher than those obtainable from the periphery of the fundus. At the same time, however, there may be a wide difference between the concentrations of fundus specimens taken from the central portion of the fluid contents and from the layer adjacent to the mucosa. If one considers a rapid transfer of fluid and possibly dissolved substances to occur through the gastric

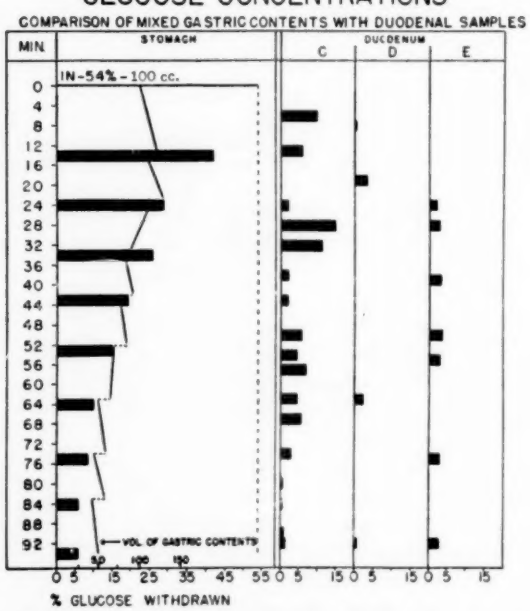

CHART 2.—The effect of a changing intragastric volume and concentration of glucose solution upon the concentration of the duodenal contents. At each time interval the stomach contents was completely removed, measured and all but a sample for analysis reinjected.

lining, the layer next the epithelium itself would be the one of lowest concentration. A peristaltic wave advancing along the conical antrum toward the pylorus will propel glucose solution toward a region of progressively diminishing diameter. The ratio of mucosal area to chyme volume momentarily increases. The fluid in the center of the antrum is forced orad, since it cannot advance, while, when the pylorus finally opens, it is the dilute peripheral layer of gastric contents which enters the duodenal cap. Since it has been impossible so far to recover this layer from the gastric side save in operated animals we feel that in the human the

duodenal cap contents represent the true character of the gastric content as it is expelled from the stomach. The fact that the stomach does not put out glucose in amounts proportional to the concentration administered has long been known, but the rôle of the shape of the viscera in modifying the flow of contents as distinct from any selective reflexes has not been emphasized.

General Discussion. The results given above are of interest chiefly for two reasons: 1, They probably represent the changes taking place in the upper digestive tract of normal man after the eating of sweets, and 2, they indicate the remarkable extent to which the major portion of the small gut is protected from wide variations in the character of its contents. These observations on man are of interest in relation to observations carried out by other workers on animals. Auchinachie, Macleod and Magee[2] have observed that in excised intestine $\frac{3}{4}$ molar (13.5%) was the concentration of glucose that most rapidly traversed the gut wall. Magee and Reid,[8] carrying on this study *in vivo*, found indications that this concentration likewise is that at which glucose solutions most rapidly leave the stomach and enter the blood stream. Table 4 indicates the highest intestinal glucose concentration obtained by

TABLE 4.—PREVIOUSLY REPORTED FIGURES ON GLUCOSE CONCENTRATIONS.

		Glucose.		
Authors.	Animals.	Concentration into stomach (%).	Highest concentration out of intestine (%).	Time (hrs.).
Ravdin, Johnston and Morrison[10]	Dog	50	5.3	1
Cori[3]	Rat	80	14.2	3
Donhoffer[4]	Rat	76–18	12–8	1
Magee and Reid[8]	Rat	54	7.5	1–2
Macleod, Magee and Purves[7]	Rat	54	11.4	2

workers on intact animals after the introduction of solutions into the stomach. While Ravdin, Johnston and Morrison[10] recovered relatively low concentrations, the significant fact is that the highest concentration recovered by anyone was 14.2%. With these findings our observations upon the normal human stomach and intestine are in complete agreement and it would therefore appear that a concentration of 12% to 15% or about $\frac{3}{4}$ molar, which incidentally is about the maximal concentration of glucose naturally occurring outside a bee tree, must be exceeded before gastric emptying is delayed and the stomach forced to play a part in the reduction of the concentration of its contents.

Conclusions. 1. There is no appreciable delay in the entry of glucose into the duodenum after the ingestion of a concentrated solution.

2. Following the ingestion of glucose solutions a far greater proportion of the sugar is absorbed from the gastro-duodenal region than from the jejuno-ileal region.

3. The range of glucose concentration from the cardia to the upper jejunum is from the concentration ingested to approximately 4% to 6%.

4. The maximal concentration at which glucose solutions usually enter the duodenum is 15% or less.

REFERENCES.

(1.) **Abbott, W. O., Karr, W. G.,** and **Miller, T. G.**: (*a*) Am. J. Digest. Dis. and Nutr., **4**, 742, 1938; (*b*) Am. J. Med. Sci., **191**, 874, 1936. (2.) **Auchinachie, D. W.**: **Macleod, J. J. R.,** and **Magee, H. E.**: J. Physiol., **69**, 185, 1930. (3.) **Cori, C. F.**: J. Biol. Chem., **66**, 691, 1925. (4.) **Donhoffer, S.**: Arch. f. d. ges. Physiol., **235**, 568, 1935. (5.) **Hoffman, O. D., Abbott, W. O., Karr, W. G.,** and **Miller, T. G.**: J. Biol. Chem., **123**, lvii, 1938. (6.) **Karr, W. G.,** and **Abbott, W. O.**: J. Clin. Invest., **14**, 893, 1935. (7.) **Macleod, J. J. R., Magee, H. E.,** and **Purves, C. B.**: J. Physiol., **70**, 404, 1930. (8.) **Magee, H. E.,** and **Reid, E.**: Ibid., **73**, 163, 1931. (9.) **Pendergrass, E. P.**: Personal communication. (10.) **Ravdin, I. S., Johnston, C. G.,** and **Morrison, P. J.**: Proc. Soc. Exp. Biol. and Med., **30**, 955, 1933.

INTUBATION STUDIES OF THE HUMAN SMALL INTESTINE.

XIV. THE ABSORPTION OF GLUCOSE FROM THE DUODENUM.*

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Previous investigation in this clinic[2] has shown that when a glucose solution is administered by mouth to a normal human subject only a small part of it reaches the duodeno-jejunal junction. The remainder presumably is absorbed in the stomach, the duodenum or both. In an attempt further to localize the place of disappearance the absorptive capacity of the duodenum alone for glucose has been studied with the results hereinafter recorded.

Method. Previous experience in quantitative studies of intestinal absorption in man had convinced us that the duodenum is the most difficult region of the entire digestive tract to isolate by mechanical means because of its great activity, its wide range of internal pressures and the ease with which its motor function is disturbed by extrinsic factors. It was necessary, therefore, to take unusual precautions for accuracy, including a very complicated apparatus and the selection of especially well-trained professional subjects.

* Aided by grants from the Committee on Scientific Research of the American Medical Association, and from Smith, Kline and French Laboratories.

Subjects. Four normal women who had served as paid subjects for many other complicated experiments were selected. They were emotionally stable and had had a careful history, physical examination, gastric analysis and barium meal to establish their normal status. Their ages, weights, heights and surface areas are recorded in Table 1. No food or fluid was allowed for at least 9 hours before the experiment.

Apparatus. An arrangement of tubes was used which enabled us to maintain a constant flow of solution of known concentration into the duodenum and to recover all that was not absorbed. A device composed of 4 tubes was usually employed (Fig. 1). Tube D was of $\frac{1}{32}$ inch outside

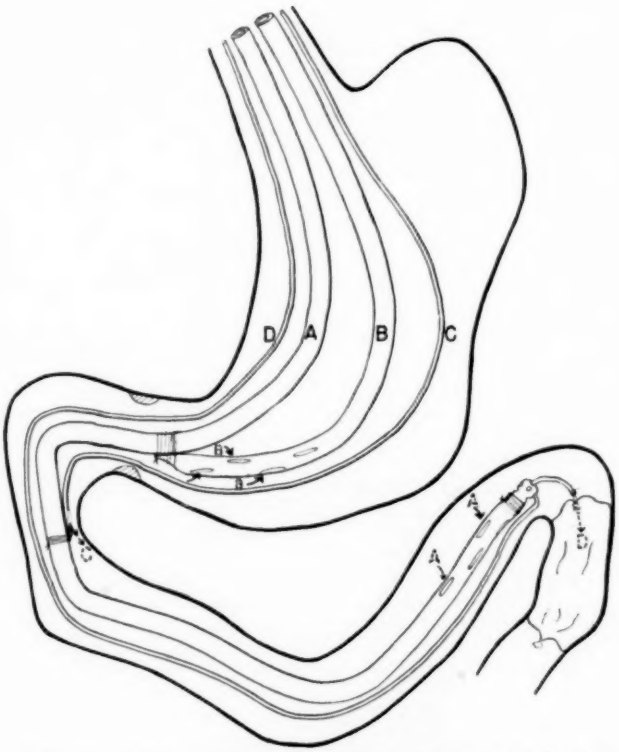

FIG. 1.—Diagram of the apparatus used in studying the rate of duodenal absorption. (See "Procedure" in text.)

diameter and $\frac{1}{64}$ inch inside diameter and led to a thin rubber balloon *D* capable of holding 50 to 100 cc. of air. Tube A was of 5.3 mm. outside diameter and ended at the balloon *D*. For its last 3 cm. it was perforated with many holes *A*. Tube C, the same size as D, was fastened to Tube A. Its opening *C* lay 15 cm. proximal to the balloon *D*. Tube B, the same size as Tube A, ended 5 cm. proximal to C and was perforated with many holes for the last 15 cm. of its length.

Procedure. The technique employed was ordinarily as follows, minor variations being adopted when they were indicated. With the balloon deflated, the tubes were swallowed and by fluoroscopic manipulation they

were so placed that the balloon *D* lay just distal to the duodeno-jejunal junction, the Tube A ended at the ligament of Treitz, the opening *C* lay in the descending duodenum and the Tube B ended at the pylorus but sagged into the most dependent portion of the stomach. The subject lay supine on a fluoroscopic table, the head of which was raised to approximately 60° from the horizontal. All fasting contents of the stomach and duodenum were aspirated and thereafter constant suction, maintained at −100 cm. of water, was applied to Tubes A and B. Balloon *D* was then inflated to occlude the jejunum. A 300 cc. test solution of 15% glucose in warm water was injected through Tube C at a rate of 10 cc. per minute. At 5-minute intervals a fluoroscopic tracing on celluloid was made of the exact position of the tubes. At the end of 30 minutes the stomach and duodenum were washed out with the utmost rapidity in the following order. Into Tube A 50 cc. of water were rapidly injected and withdrawn. At the same time 250 cc. of water were quickly swallowed and aspirated from the stomach by Tube B. Into Tube C 50 cc. of water were injected and recovered from Tubes A and B. All tubes were then withdrawn slowly, constant suction being maintained on Tubes A and B as they came out. If the withdrawal caused vomiting the vomitus was saved.

Table 1.—Experimental Subjects—Personal Data.

Subject.	Age (years).	Height (inches).	Weight (lbs.).	Surface area (sq. M.).
Hn.	34	66½	216	2.08
Hl.	35	65	129	1.63
Pr.	43	66½	180	1.90
Ps.	46	64	124	1.58

The absorption by the duodenum was calculated as follows: From the glucose given, the total amount recovered by all routes was subtracted. The jejunal peristalsis during the half-hour absorption period sometimes drew the balloon several centimeters into the jejunum, pleating the gut on the tube and exposing the sugar solution to jejunal mucosa. From the tracings of the tube at each 5-minute fluoroscopy the ratio of the length of the duodenum to the length of the exposed portion of the jejunum was determined. The total absorption was apportioned to the duodenal and the jejunal units in proportion to the average ratio. It is realized that the rate of absorption is probably somewhat greater in the duodenum than in the upper jejunum and that where much of the jejunum was included in the absorption area an error is introduced by this method of calculation. However, the consistency of the results appear to justify its use.

So many sources of technical error were possible in this procedure that it was felt wiser to vary the details of the process frequently, lest some undetected constant error warp the findings. As none of them appears to have had a significant effect upon the results the typical procedure only has been given.

Results. From 20 experiments 13 were selected as being technically satisfactory. The results of these (Table 2) show an absorption capacity for the duodenum of from 6.3 to 19 gm. per hour.

Discussion. The point of this procedure was to keep the duodenal mucosa constantly bathed with a fresh solution of glucose throughout a stated period, so that an excess of sugar should always be present at as nearly a known concentration as possible. The wide variation in absorption figures is interesting from the standpoint of individual variations. The lowest figure, 6.3 gm. per hour,

occurred on an occasion when Ps. was given a 5% solution. From the same solution Pr. absorbed twice as much, while from a 10% solution Hn. absorbed 1.9 gm. per hour more than the highest absorption rate attained by Pr. from a 15% solution. Nevertheless, though Hn. took up 19 gm. per hour from a 10% solution on 1 day, she only absorbed 8.5 gm. per hour from a 15% solution at another time. While these variations would occur, were we failing to recover all the unabsorbed glucose injected, we have come in the course of time and by virtue of many carefully controlled experiments to feel that under the circumstances of these selected experiments no glucose solution was escaping past the balloons. We are prepared then to believe that people have their good days and their bad days and that the rate of glucose absorption is rather variable from time to time in the same individual.

TABLE 2.—DUODENAL ABSORPTION OF GLUCOSE.

Subject.	Glucose given.		Absorption time (minutes).	Total absorption (gm./hr.).	D/J* length ratio (%).	Duodenal absorption (gm./hr.).
	%.	Gm.				
Pr. . . .	5	15	23	17.8	71	12.6
Hn. . . .	5	15	30	11.8	83	9.8
Ps. . . .	5	15	32	8.8	72	6.3
Ps. . . .	5	15	32	12.5	61	7.6
Hn. . . .	10	30	30	25.0	65	15.8
Pr. . . .	10	25	29	32.8	29	9.2
Hn. . . .	10	24	27	19.0	100	19.0
Hl. . . .	15	15	30	11.7	100	11.7
Pr. . . .	15	45	27.5	15.2	50	7.6
Hn. . . .	15	45	30	21.6	60	12.9
Pr. . . .	15	19.5	24	20.0	57	11.4
Hn. . . .	15	15	21	21.1	40	8.5
Pr. . . .	15	37.5	27.5	28.8	56	17.1

* Duodenal/jejunal.

This series of experiments would appear to be sufficient to warrant the conclusion that if the duodenum receives its normal concentration of glucose—shown by previous studies to be not over 15%—then 20 gm. per hour would usually represent the maximal absorption capacity of the duodenum.

Although the experiments here recorded are not strictly comparable to those by which we studied the absorption rate of the lower small gut,[1] it appears that the duodenum absorbs glucose appreciably more rapidly than do the jejunum and the ileum. While we have no evidence on the relative power of the individual epithelial cells to perform this function at the different intestinal levels, the studies of Warren[3] on the relation of the intestinal length to the mucosal surface area suggest that the observed differences in the absorption rate may be due simply to the greater number of epithelial cells per unit length of gut at the proximal as compared to the distal end of the intestine.

The implications of these experiments with regard to the areas proximal to the duodeno-jejunal junction from which glucose is absorbed is their chief importance. It becomes immediately apparent in reviewing experiments in which glucose given by mouth is recovered from the beginning of the jejunum that more glucose has been absorbed proximal to that point than could be removed by a duodenum absorbing 19 gm. per hour.[2] While this is only true in those instances in which solutions of high concentration are given, it forces a consideration of the question of gastric absorption. Attempts to obtain direct evidence on this point are recounted in another paper.

Summary. 1. The duodenum absorbs glucose very rapidly as compared to other regions of the alimentary canal of equal length and at a rate that varies in the individual from day to day.

2. Though as little as 6 gm. per hour has been absorbed from dilute solutions, the maximal rate from solutions within the normally occurring concentration range is about 20 gm. per hour.

REFERENCES.

(1.) **Abbott, W. O., Karr, W. G.,** and **Miller, T. G.**: Am. J. Digest. Dis. and Nutr., **4**, 742, 1938. (2.) **Karr, W. G., Abbott, W. O., Hoffman, O. D.,** and **Miller, T. G.**: Am. J. Med. Sci, **200**, 524, 1940. (3.) **Warren, R.**: Anat. Rec., **75**, 427, 1939 (also suppl).

CLINICALLY ASSOCIATED DEFICIENCY DISEASES.*

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The period during which brilliant investigations led to the isolation, synthesis and clinical evaluation of thiamin, nicotinic acid, riboflavin, and vitamin B_6 has been followed by one of confusion. The literature in regard to these vitamins and the deficiency diseases arising from a lack of them is vast and often contradictory. Continued research concerning the members of the vitamin B complex and their relation to deficiency states and to each other is necessary for the problem is complex and precise knowledge is meager (Fig. 1). Nevertheless, our studies of clinically associated deficiencies indi-

* The heavy burden of expenses necessary for this work has in large part been borne by the John and Mary R. Markle Foundation, Anhaeuser-Busch, Inc., and Eli Lilly and Company.

cate that the application of certain principles and methods of therapy is followed by spectacular improvement in the health and well-being of these persons.

The present report is concerned with studies conducted in Jefferson County, Alabama, and Hamilton County, Ohio. In a series of 1250 consecutive malnourished persons, we have studied the predisposing causes, development, early diagnosis and specific therapy of nutritional diseases. The studies reported in this communication were begun February 1, 1938, and extended through April 30, 1940. They are being continued, but the results to date are such as to warrant the following report.

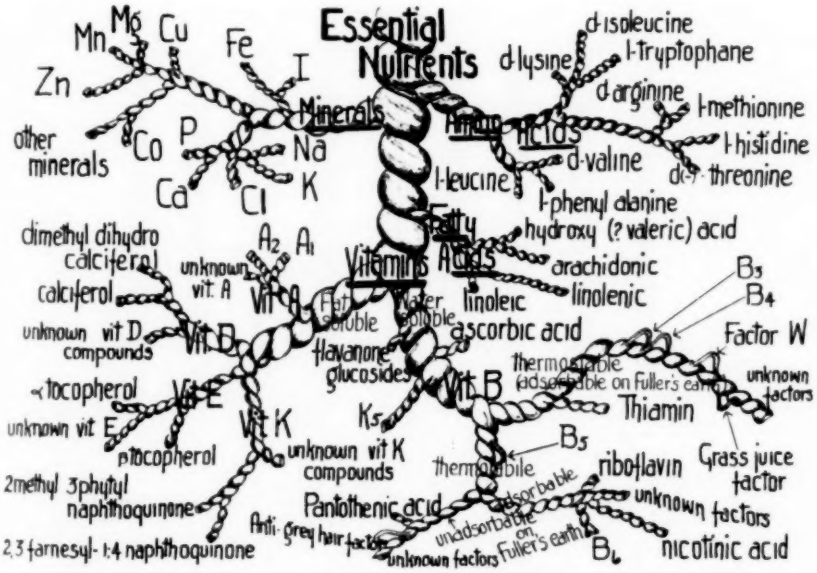

FIG. 1.—Differentiation of some of the essential nutrients. It seems especially pertinent to separate the fat-soluble and water-soluble vitamins. Some are known only by physiologic properties and few as yet have been shown to be specific for human diseases.

Method. The subjects were selected from persons presenting themselves for examination either at the Hillman Hospital, Birmingham, Ala., or the General Hospital, Cincinnati, Ohio. The patients made frequent visits to the clinic, and at the time of each visit they were weighed, examined, and medical and dietary histories were taken. Home surveys of 50 cases were made to ascertain what the patients actually ate. As soon as a diagnosis of nutritional deficiency was made, responsibility was immediately assumed and study begun. The diagnosis of a specific deficiency state was based on the presence of symptoms characteristic of it. For example, a diagnosis of pellagra was made only if characteristic mucous membrane lesions, dermal lesions, or both, were present; a diagnosis of riboflavin deficiency depended upon the presence of characteristic angular lesions of the mouth,

or ocular symptoms; a diagnosis of beriberi was made only in the presence of nutritional neuritis. The diagnosis in each instance was confirmed by the response of the patient to the specific therapeutic agent, administered under controlled conditions. In general, the method of confirmation consisted in the dramatic response of the patient to the administration of synthetic nicotinic acid or its compounds, synthetic riboflavin, or synthetic thiamin hydrochloride, or synthetic vitamin B_6 the patient's diet remaining constant. Many of these patients had other diseases, such as scurvy, which was treated with synthetic cevitamic acid, and vitamin A deficiency, which responded to carotene or oleum percomorphum. Some of the patients after being treated with specific therapeutic agents were given either liver extract or dried brewer's yeast as supplements to their diets.

AVERAGE DIET OF FIFTY PELLAGRINS COMPARED WITH ADEQUATE DIET.

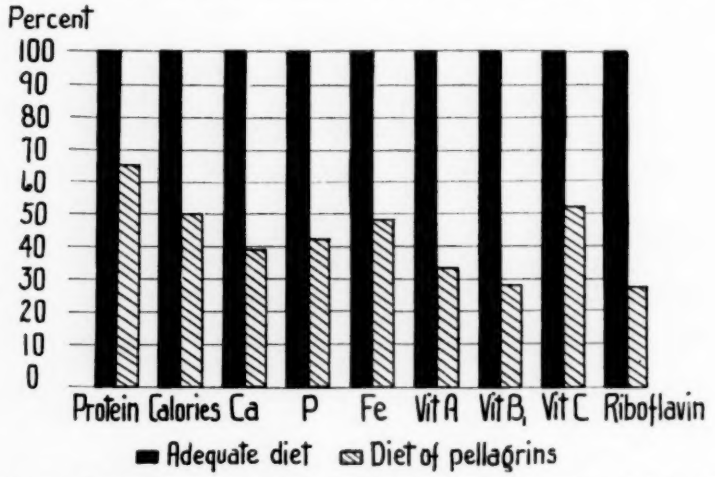

FIG. 2.—These dietaries are typical of those used by other members of the family and by neighbors who did not have clinical pellagra during the course of the study.

Observations. *Dietary.* That general malnutrition must be present in many of these persons even though they have no symptoms of a specific deficiency disease is indicated by a detailed analysis of the dietaries of 50 cases which shows that they are deficient to some extent in each of the essential nutrients. An accurate record of all the food eaten by each patient was kept for a period of 1 week. During this time, frequent visits to the home were made to determine the size of the portions of food used and the method of preparing it. Using the most accurate available information on the composition of foods, the total content of calories, vitamins, protein, and minerals in the food consumed by each patient in 1 week was calculated, and from this the average daily intake was determined. The nicotinic acid and vitamin B_6 content of foods is too little known to warrant evaluating the dietaries in respect to these vitamins.

Human nutritional requirements cannot be stated with absolute precision, but Stiebeling has estimated the quantities of nutrients required daily by the average individual; we may thus assess approximately the deficiencies in the dietaries of these persons (Fig. 2).

1. *Calories.* The average person received only 50% of his estimated energy requirement.

2. *Protein.* The protein intake of the average individual in this group was 35% below the desirable amount. The average intake of 0.68 gm. per kilo of body weight was above the maintenance requirement of 0.5 gm. per kilo calculated by Sherman, but did not approach the 1 gm. per kilo which is recommended as a liberal daily allowance; this optimum level was reached by only 5% of the patients. On the other hand, 35% of them received less than 0.5 gm. per kilo and were undoubtedly suffering from the effects of this low nitrogen intake.

Mitchell has shown that lysine and tryptophane are limiting factors in the growth of young animals receiving their protein entirely from whole corn, and that lysine is a limiting factor in the case of wheat flour. In the majority of these 50 dietaries, a large part of the total protein was furnished by grain products, and if the remainder of the protein were also low in lysine and tryptophane content, a specific deficiency of these two amino acids might be expected. In three-fourths of the cases studied, however, more than 10% of the total protein came from animal sources and was of excellent biologic quality. Sherman has shown that such a mixture of grain and animal proteins is adequate for nitrogen equilibrium in adults even at low levels of intake. The remaining fourth of the patients ate enough vegetables to supply an average of 35% of their total protein intake. The proteins of many vegetables are inferior in biologic value when fed as the sole source of nitrogen; Mitchell has shown that this is due to a low content of the sulphur-containing amino acids in the case of navy beans, garden peas, and potatoes. It is likely, however, that vegetable proteins supplement those of grain products to some extent.

The total protein intake in at least 35% of the cases studied is too low to maintain nitrogen equilibrium. Whether this results in a specific or a general amino-acid deficiency is uncertain.

3. *Minerals.* Nearly all the patients received sub-standard amounts of calcium, phosphorus and iron, and none of them obtained standard amounts of all three elements. In two-thirds of the 50 cases, the intake of these minerals was not sufficient to meet even the maintenance requirement. About 72% of the patients were probably losing calcium and phosphorus. Although iron deficiency was less marked than that of calcium and phosphorus, 64% received less than 8 mg. of iron daily with an average intake of 4.8 mg.; 10% obtained less than 4 mg. daily. Undoubtedly such

restricted iron intake, if continued long enough, will predispose to anemia.

4. *Vitamins.* Suboptimal amounts of all the vitamins were furnished by the dietaries examined. The average diet fell below the suggested standards for normal persons approximately as follows: vitamin A, 67%; vitamin B_1, 72%; vitamin C, 47%; and riboflavin, 73%. From these results, it appears that the deficiency of vitamin C is not as marked as that of the other vitamins. It must be remembered, however, that these figures represent the average intake of the group. Several individuals consumed diets in which there were no foods containing vitamin C.

An examination of these dietaries leaves little doubt that patients subsisting on them are malnourished and prone to develop mixed deficiencies.

Clinical. There was great improvement in every person treated. Approximately 30% were able to obtain positions and work steadily, whereas they had previously had years of ill-health which interfered with their ability to work. Following the administration of nicotinic acid or nicotinic acid amide, or other potent substances related to this compound, there was prompt disappearance of the mucous membrane lesions of pellagra, healing of the dermal lesions, and disappearance of the mental symptoms due to pellagra. There was also an increase to normal or above in the concentration of Coenzymes I and II in the blood, and disappearance of abnormal pigments in the urine. Following the administration of vitamin B_1, there was improvement in the patient's general condition and prompt amelioration of the symptoms arising from neuropathy or edema. The administration of riboflavin caused the disappearance of the dermal lesions and ocular symptoms characteristic of riboflavin deficiency within a week. The administration of synthetic vitamin B_6 was followed by prompt disappearance of the extreme nervousness, insomnia, irritability and abdominal pain, and the patients were able to walk without difficulty. A number of the patients were treated successfully for anemia, scurvy, and vitamin A deficiency. As a rule, there was prompt improvement in the syndrome for which the chemical substance is specific following its administration, whereas the symptoms of associated syndromes did not improve so long as the diet remained constant.

Although the administration of a single chemical substance was followed by a remarkable response of the lesion for which it was specific and by a great increase in the patients' strength, the improvement of the patients in general was greater when they were given a number of synthetic materials than when they were given any one alone. Furthermore, when supplements of dried brewers' yeast powder (Anhaeuser-Busch, Inc., Mead Johnson and Company, and the Harris Laboratories, Inc.) or liver extract (Eli Lilly and Co.) were given in addition to synthetic materials to persons who con-

tinued to eat their usual inadequate diets, there was an even greater improvement in their general health.

Summary and Conclusions. Twelve hundred and fifty persons with clinically associated deficiency disease syndromes have been treated without a fatality, whereas the mortality rate a few years ago was 54%. The clinical studies of these persons and analysis of their diets indicate that they have a deficiency in calories, protein, calcium, phosphorus, iron, and the known vitamins. They have mixed rather than single deficiency diseases, and months and years of ill-health precede any diagnostic lesions of a specific deficiency. Part of the confusion in the literature regarding vitamins and deficiency diseases is due to the discovery that vitamin B, which was formerly considered a single substance, is composed of 12 or more separate factors, each, together with unknown substances, contributing to the total effect of therapeutic agents such as yeast, wheat germ, or liver extract. These studies suggest that from the standpoint of practical application, mixed vitamin therapy is often desirable. In our hands, the administration of water-soluble vitamins, together rather than individually, and the fat-soluble vitamins, together rather than individually, has a definite usefulness in our day to day treatment of these deficiency states.

Invaluable aid was given by the administrative and professional staffs of the General Hospital and the Hillman Hospital, and we are particularly indebted to Drs. R. W. Vitler, W. B. Bean, C. D. Aring, H. S. Schiro, J. B. McLester, S. L. Applebaum, D. P. Hightower, L. H. Hubbard, T. S. Booser, A. W. Woods, J. P. Frostig, H. E. Himwich, and F. H. Lewy. Technical assistance was given by Mrs. S. P. Vilter and Mrs. M. B. Koch; and nursing service, by Mrs. A. W. Mann, Miss Monette Springer, and Miss Verna Moore.

VITAMIN C IN EPILEPSY.

DILANTIN SODIUM NOT A CAUSE OF VITAMIN C DEFICIENCY.*

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ONE of the side effects in patients with epilepsy who are being treated with dilantin sodium is swelling of the gums. This swelling is a benign hyperplasia and in most instances is not noticed by the patient. Kimball[5] reported this gingival hyperplasia in 57% of his patients and expressed the belief that it was due to a deficiency

* The study was aided by a grant from the Parke, Davis & Company.

in vitamin C induced by the drug. He did not offer adequate evidence for this hypothesis since none of the other symptoms of scurvy were present and the average vitamin C content of the plasma of patients who had gingival hyperplasia was not lower than would be expected in his patients, who were pupils in the Detroit free school for epileptics and were from the lower economic levels of society. In addition, his administration of large amounts of vitamin C produced no change in the abnormal condition of the gums even though the plasma vitamin C content was raised thereby to well above the normal level. Gruhzit,[3] working with animals, found that the administration of dilantin sodium had no effect on the absorption or utilization of vitamin C. The occurrence of prominent swelling of the gums in about 3% of our patients under treatment with dilantin sodium led us to make a study of the vitamin C content of the plasma of as many of our patients with convulsive seizures as possible, regardless of the type of therapy being administered.

Method and Results. Venous blood was withdrawn from the patients and the vitamin C content of the plasma determined by the method of Farmer and Abt.[2] The protein-free filtrate was made within 15 minutes of withdrawal of blood, and the titrations performed within 2 hours.

Determinations were made on the plasma of 257 patients. The majority of these determinations were on ambulatory patients attending the outpatient department of the Boston City Hospital. The remainder were on private patients. None were taking a special diet. The results obtained are grouped with reference to the type of therapy which the patients had been receiving and are shown in Table 1.

TABLE 1.—THE VITAMIN C CONTENT OF THE PLASMA OF PATIENTS WITH "EPILEPSY."

Type of medication.	No. of patients.	No. of determinations.	Vitamin C content of plasma (in mg. per 100 cc.).		
			High.	Low.	Average.
None	31	32	1.2	0.05	0.46
Phenobarbital	44	47	1.6	0.00	0.45
Dilantin sodium	182	207	1.6	0.05	0.44

The range of the plasma levels of vitamin C and the average value for the three groups of patients receiving: 1, no treatment; 2, phenobarbital; and, 3, dilantin sodium, respectively, were almost identical.

To determine whether the long continued administration of dilantin sodium had any effect on the vitamin C level of the plasma, the results in 182 patients receiving this medication were divided into groups with reference to the length of time each group had been receiving it. The results as shown in Chart 1 indicate that there was no appreciable difference in the vitamin C content of the plasma of patients who had been taking dilantin sodium for 2 years from that of the patient who had never received this medication. To

further check this observation, the determination was repeated in 25 patients after 5 months of treatment. The results were identical in 8, there was a slight or moderate increase of vitamin C in 10, and a slight or moderate decrease in 7 patients.

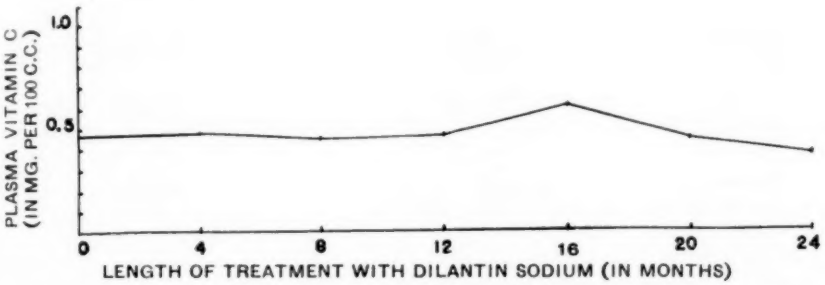

CHART 1.—The relationship of the vitamin C content of the plasma to the length of treatment with dilantin sodium.

Forty of the 182 patients (22%) who were receiving dilantin sodium therapy had some degree of gingival hyperplasia which was not present before treatment began. In only 5 patients (3%) was the swelling severe enough to cause discomfort. The vitamin C content of the plasma bore no relationship to the presence or absence of this symptom (Table 2). The average content in the 40 patients with swollen gums (0.44 mg. per 100 cc.) was exactly the same as that of the 142 patients without this symptom.

TABLE 2.—THE RELATIONSHIP OF THE VITAMIN C CONTENT OF THE PLASMA TO THE DEGREE OF GINGIVAL HYPERPLASIA IN PATIENTS UNDER TREATMENT WITH DILANTIN SODIUM.

Severity of gum swelling.	No. of patients.	Vitamin C content of plasma (in mg. per 100 cc.).		
		High.	Low.	Average.
None	142	1.66	0.05	0.44
Mild	20	1.10	0.10	0.40
Moderate	15	1.30	0.10	0.50
Severe	5	0.76	0.12	0.40

TABLE 3.—THE EFFECT OF THE ADMINISTRATION OF FOODS HIGH IN VITAMIN C CONTENT ON THE PLASMA VITAMIN C LEVEL IN 16 PATIENTS UNDER TREATMENT WITH DILANTIN SODIUM.

	Vitamin C content of plasma (in mg. per 100 cc.).		
	High.	Low.	Average.
Before	0.62	0.07	0.22
After	1.77	0.43	1.12

To test the effect of administration of vitamin C by mouth on the plasma vitamin C content of patients under dilantin sodium therapy, 16 patients with a low level were requested to eat 4 oranges and drink a glass of tomato juice daily for periods ranging from 1 to 2 months while continuing the use of dilantin sodium. There was a prompt rise in the plasma content of all of these patients from an

average level of 0.22 to 1.12 mg. per 100 cc. (Table 3). The swelling of the gums which was present in 12 of these 16 patients was not affected by this diet.

Discussion. The vitamin C content of the plasma of apparently healthy individuals on a well balanced diet is usually between 0.8 and 1.2 mg. per 100 cc. The results of determinations in large numbers of individuals with no signs or symptoms of scurvy show a variation over a much wider range,[7] and it may be stated that the vitamin C content of the plasma of an individual represents the relative dietary intake of vitamin C in the preceding few weeks. Because foods rich in vitamin C are relatively expensive, it is not surprising that the plasma vitamin C content of patients in the low economic groups or in institutions for the care of the mentally or chronically ill[1,8,9] is much lower than that usually reported as normal. In our group of patients the average value (0.45 mg. per 100 cc.) was only half of the lower limit of normal but this value is similar to that reported by Lund[6] for patients admitted to the surgical service of this hospital and in agreement with the reports from hospitals for chronically ill patients. The average value for the 23 private patients in our group who were taking dilantin sodium was 0.8 mg. per 100 cc. This is further evidence that the level of vitamin C in the plasma is influenced by economic factors. Herlitz[4] studied hyperplastic gingivitis in dental patients with no symptoms of scurvy and found no relationship between the gingivitis and the vitamin C content of the plasma.

Summary. 1. The plasma vitamin C content of 257 ambulatory patients with convulsive seizures varied between 0.0 mg. and 1.6 mg. with an average of 0.45 mg. per 100 cc.

2. The plasma vitamin C content of these patients was in no way influenced by the type of therapy they were receiving.

3. The long continued administration of dilantin sodium had no effect on the vitamin C level of the plasma and did not influence the absorption of vitamin C when given by mouth.

4. Hypertrophic gingivitis developing in patients under treatment with dilantin sodium is not related to the vitamin C content of the plasma or to the utilization of vitamin C.

5. The low level of vitamin C in the plasma of clinic patients with epilepsy is due to an inadequate intake of this element, because the administration of food with a vitamin C content to a group with low values resulted in a 5-fold increase.

REFERENCES.

(1.) **Alexander, L., Pijoan, M., Schube, P. G.,** and **Moore, M.**: Arch. Neurol. and Psychiat., **40**, 58, 1938. (2.) **Farmer, C. J.,** and **Abt, A. F.**: Proc. Soc. Exp. Biol. and Med., **32**, 1625, 1935; Ibid., **34**, 146, 1936. (3.) **Gruhzit, O. M.**: Arch. Path., **28**, 761, 1939. (4.) **Herlitz, C. W.**: Acta Paediat., **24**, 341, 1939. (5.) **Kimball, O. P.**: J. Am. Med. Assn., **112**, 1244, 1939. (6.) **Lund, C. C.**: New England J. Med., **221**, 123, 1939. (7.) **Meikeljohn, A. P.**: Ibid., **220**, 518, 1939. (8.) Vitamin C in State Hospital Patients and Personnel, Elgin Papers, **3**. 225, 1939. (9.) **Wortis, H., Liebman, J.,** and **Wortis, E.**: J. Am. Med. Assn., **110**, 23, 1896, 1938.

BOOK REVIEWS AND NOTICES

THE EMPEROR'S ITCH. The Legend Concerning Napoleon's Affliction With Scabies By REUBEN FRIEDMAN, M.D., Assistant Professor of Dermatology and Syphilology, Temple University School of Medicine, Philadelphia. Pp. 89; 10 illustrations. New York: Froben Press, 1940. Price, $1.50.

THE author discusses the legend of Napoleon having been affected with scabies. He suggests that Napoleon may have had dermatitis herpetiformis, and it is not surprising that his evidence for this is unconvincing, since the diagnosis of this disease often presents difficulty in living patients. Portions of the book are interesting, but its publication as a monograph hardly seems justified. D. P.

DERMATOLOGIC THERAPY IN GENERAL PRACTICE. By MARION B. SULZBERGER, M.D., Assistant Clinical Professor of Dermatology and Syphilology, Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital of Columbia University; Associate Attending Dermatologist, Montefiore Hospital, New York City, and JACK WOLF, M.D., Attending Dermatologist and Syphilologist, Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital of Columbia University; Director of Dermatology, New York City Cancer Institute. Pp. 680; 65 illustrations and 25 tables. Chicago: The Year Book Publishers, Inc., 1940. Price, $4.50.

IN this volume the authors have set down in concise, clear, and detailed fashion the methods of dermatologic therapy which seem best and most effective for use by the physician not especially trained in dermatology. They discuss only those diseases which are relatively common and "make up perhaps 90 per cent of all dermatologic cases." They have properly omitted the details of special and complex methods of treatment which may best be carried out by the dermatologist or the dermatologically-minded roentgenologist, surgeon, or allergist.

The senior author, in particular, has for the past decade been establishing himself as a competent experimenter in dermatology and as one of the most literate and intelligent interpreters of changes of the skin in the light of immunologic and other basic physiologic studies. It is immediately apparent that the authors do not regard the prescribing of lotions and ointments as the more important part of skin therapy. Proper emphasis is laid upon the methods of obtaining an intelligent and searching history and of examining the skin, upon the rationale of allergic study (with justifiable indication of the ineptness of much of the ordinarily employed scratch and intradermal test methods in urticaria and contact dermatitis), upon the value of a general medical approach to many dermatoses, and upon the easily available methods of laboratory diagnosis. The illustrated instructions for the application of local medication of varying types to different parts of the skin and the many practical details for increasing the acceptability of messy methods of treatment are extremely valuable. Reference is made to many useful proprietary medicines and foods, always with a helpful indication of where these preparations may be obtained.

As in other fields of medicine, a considerable portion of dermatologic treatment is on an empiric basis, and it is inevitable that the informed reader will disagree on some minor points. For example, the inclusion of

manganese injections and of tin salts orally in the list of treatments for acne can hardly be endorsed. The occasional essential importance of orthopedic measures in the treatment of plantar warts is not mentioned. The section on syphilis is brief and does not approach in completeness those on dermatologic therapy. The tone of personal authority is lacking in this chapter, and to this Reviewer its inclusion in a book on dermatologic therapy seems unnecessary and anachronistic.

The volume cannot fail to be extremely valuable to the specialist in dermatology as well as to the general practitioner. While its broad classification of dermatoses is simple, the extremely helpful differential diagnostic lists and discussions include many terms which imply a reasonably good working knowledge of dermatology on the part of the reader. However, as the authors state, this book is not offered as a complete text, but as a supplementary practical source of information which, to this Reviewer's knowledge, is not available in any other single volume. It is a credit to the authors and to the field of dermatology. D. P.

OBSERVATIONS MADE DURING THE EPIDEMIC OF MEASLES ON THE FAROE ISLANDS IN THE YEAR 1846. By PETER LUDWIG PANUM, M.D. (Translated from the Danish by ADA SOMMERVILLE HATCHER). With a Biographical Memoir by JULIUS JACOB PETERSEN, M.D. (Translated from the Danish by JOSEPH DIMONT), and an Introduction by JAMES ANGUS DOULL, M.D. Pp. 111. Published by the Delta Omega Society. Distributed by the American Public Health Association, New York City, 1940. Price, $2.50.

THE Delta Omega Society has from time to time sponsored the republication of public health classics that are not generally available to students of public health. The present volume is Panum's report upon the epidemic of measles in the Faroe Islands, one of the most famous and complete of all epidemiologic studies. Brought to the highly susceptible population of the Faroes by an islander on his return from Copenhagen, measles attacked 97% of the inhabitants, resulting in some 5000 cases and 102 deaths. The first medical writing of its young author, the report remains a masterpiece that makes fascinating reading nearly a century after its appearance. The Delta Omega Society is to be congratulated upon its selection. R. K.

GYNECOLOGICAL AND OBSTETRICAL PATHOLOGY. With Clinical and Endocrine Relations. By EMIL NOVAK, A.B., M.D., D.Sc. (Hon. Dublin), F.A.C.S., Associate in Gynecology, The Johns Hopkins Medical School; Gynecologist, Bon Secours and St. Agnes Hospitals, Baltimore, etc. Pp. 496; 427 illustrations. Philadelphia: W. B. Saunders Company, 1940.

FOR some years there has been a need for a well balanced presentation of gynecologic and obstetric pathology. This need has been stimulated, no doubt, by the increasing interest in endocrinology and the relation of pelvic pathology to abnormalities of the menstrual cycle. Again, the requirements in pathology by the specialty examination board has stimulated the need for a book of this type. That Dr. Novak should be the author was logical from his long interest and experience in the subject. The text is exceptionally well balanced, particularly in the correlation of the pathologic physiology of the pelvic organs and clinical symptoms. The endocrinologic aspects of the subject has been very comprehensively presented, and includes a basic chapter on normal pelvic physiology.

In a logical order the various regions—vulva, vagina, cervix and so on, are taken up *in seriatim*. The discussion of kraurosis and leukoplakia clearly differentiates these much confused lesions. The author explains

the differences in the numerous methods of grading which have been offered. He emphasizes repeatedly the importance of serial sections and minimizes the advantages of colposcopy and the Schiller tinctorial test. Three chapters are devoted to the histology of the endometrium, a summary of cyclical and pregnancy changes in endometrium and clinical symptoms of hyperplasia of the endometrium. In discussing the difficulties which often arise in diagnostic curettage, the author quotes Halban, who after examining a doubtful specimen pronounced, "not cancer but better out." The writer states that sarcoma constitutes 4.5 per cent of uterine malignancy in his laboratory. This is a larger proportion than in most institutions and may probably be due to the fact, as he states, that a very large number of serial sections are made.

In the section devoted to the pathology of the ovary, the author devotes considerable space to the more recently described tumors such as dysgerminoma, granulosathecoma and arrhenoblastoma. This detailed discussion he feels has been necessitated through a lack of any full presentation of this subject elsewhere. The basic histogenesis of one group of these tumors leads him to suggest the inclusive designation "feminizing mesenchymoma of the ovary."

In the chapter on pelvic endometriosis following an extended discussion of its pathologic and clinical characteristics, the author gives an interesting summary of the various theories of the histogenesis of this condition. Following two complementary chapters on placentation and abnormal activity of the trophoblast, the book closes with a discussion, by Dr. L. M. Hellman, of other abnormalities and diseases of the placenta and appendages.

There are 427 illustrations in this book, the majority of them are carefully selected photomicrographs, appropriately correlating points brought up in the text. The text itself is remarkably free from quotations from the literature although a short, important bibliography is appended to each chapter. This book should fulfill a well defined need, should be of undoubted value to both physicians and pathologists, as well as serving as a textbook for those about to undertake examinations of the specialty board. P. W.

THE FOOT AND ANKLE. Their Injuries, Diseases, Deformities and Disabilities. By PHILIP LEWIN, M.D., F.A.C.S., Associate Professor of Bone and Joint Surgery, Northwestern University Medical School; Professor of Orthopædic Surgery, Post-Graduate Medical School of Cook County Hospital, etc. Pp. 620; 303 illustrations. Philadelphia: Lea & Febiger, 1940. Price, $9.00.

AN excellent treatise dealing with lesions of the foot and ankle. Written in a preëminently practical manner. Profusely illustrated with clear, pertinent halftone and line drawings.

Recommended not only to orthopedists but also to surgeons and general practitioners. G. W.

ATLAS OF CARDIOROENTGENOLOGY. By HUGO ROESLER, M.D., F.A.C.P., Associate Professor of Roentgenology; Cardiologist in the Department of Medicine, Temple University School of Medicine and Hospital, Philadelphia. Pp. 124; 166 illustrations. Springfield, Ill.: Charles C Thomas, 1940. Price, $12.50.

SIXTY cardiac case reports are presented with emphasis on the radiologic aspects. Collateral clinical and laboratory data, including electrocardiograms, are also given. Noteworthy is the correlation of the radiograms with the postmortem findings in 16 cases, the hearts being appropriately sectioned or windowed in each case. The unusually large illustrations are uniformly excellent. The examples of the different conditions causing

cardiovascular deformity are well assorted, but the variety of appearances in each of the diseased states is, in the Reviewer's opinion, insufficiently illustrated to make the atlas comprehensive. The method of presentation is commendable, and despite its incompleteness, the book is highly recommended to those specially interested in radiology and cardiology.

A. M.

HEALTH IS WEALTH. By PAUL DE KRUIF. Pp. 246. New York: Harcourt, Brace & Co., 1939. Price, $2.00.

A RECORD of certain efforts in recent years to foster a national health program, together with an outline for such a plan. The author's part in these efforts is represented chiefly by a series of articles which were published in the "Country Gentleman," and which, here reprinted, constitute the bulk of the book. Written for laymen, it is frank propaganda for a cause which should also appeal to physicians. Unfortunately, as in so much propaganda literature, there is excessive use of the tremolo stop and some loose reasoning. Thus, in the proof offered for the statement that "more than half of our nation is less than half alive," are cited the two-odd million hay fever victims, as though their illness lasted all year. Nevertheless, physicians will find the book both interesting and timely. R. K.

RHEUMATIC FEVER. Studies of the Epidemiology, Manifestations, Diagnosis and Treatment of the Disease During the First Three Decades. By MAY G. WILSON, M.D., The New York Hospital and Department of Pediatrics, Cornell University Medical College, New York City. Pp. 595; 78 illustrations and 5 appendices. New York: The Commonwealth Fund, 1940. Price, $4.50.

ACCORDING to the introduction, "no attempt has been made to prepare a text book or a comprehensive critical review of rheumatic fever." Having thus disarmed her critics, the author proceeds to present the picture of rheumatic fever in a manner at once new, readable, and inclusive.

The results of statistical analysis are used to good effect, both in pointing out certain misconceptions and in establishing new relationships. Much material is condensed into tables or graphs. The chapters are brief. Frequent summarizing paragraphs and chapters assist the reader. Diagnostic procedures are fully described. The inclusion of tables for normal values makes the book a valuable source of reference. W. J.

NEW BOOKS.

Atlas of Cardioroentgenology. By HUGO ROESLER, M.D., F.A.C.P., Associate Professor of Roentgenology; Cardiologist in the Department of Medicine, Temple University School of Medicine and Hospital, Philadelphia. Pp. 124; 166 illustrations. Springfield, Ill.: Charles C Thomas, 1940. Price, $12.50. (Review p. 547.)

Rheumatic Fever. Studies of the Epidemiology, Manifestations, Diagnosis and Treatment of the Disease During the First Three Decades. By MAY G. WILSON, M.D., The New York Hospital and Department of Pediatrics, Cornell University Medical College, New York City. Pp. 595; 78 illustrations and 5 appendices. New York: The Commonwealth Fund, 1940. Price, $4.50. (Review p. 548.)

The Medical Clinics of North America (Volume 24, No. 4, Mayo Clinic Number, July, 1940). Pp. 350; 37 illustrations. Philadelphia: W. B. Saunders Company, 1940.

In addition to a 9-article symposium on endocrine therapy, this number contains 14 papers which, as usual, cover a wide variety of subjects.

The Universe Through Medicine. By J. E. R. McDonagh, F.R.C.S. Pp. 389. London: William Heinemann (Medical Books) Ltd., 1940. Price, 25s.

Your Allergy and What to Do About It. By Milton B. Cohen, M.D., and June B. Cohen. Pp. 177; illustrated. Philadelphia: J. B. Lippincott Company, 1940. Price, $1.50.

Observations Made During the Epidemic of Measles on the Faroe Islands in the Year 1846. By Peter Ludwig Panum, M.D. (Translated from the Danish by Ada Sommerville Hatcher), with a Biographical Memoir by Julius Jacob Petersen, M.D. (Translated from the Danish by Joseph Dimont), and an Introduction by James Angus Doull, M.D. Pp. 111; illustrated. New York: Delta Omega Society, 1940. Distributed by The American Public Health Association. Price, $2.50. (Review p. 546.)

The Virus. Life's Enemy. By Kenneth M. Smith, F.R.S. Pp. 176; 1 illustration. New York: The Macmillan Company, 1940. Price, $2.00.

The Fundamentals of Nutrition. By Estelle E. Hawley, Ph.D., and Esther E. Maurer-Mast, M.D., University of Rochester School of Medicine and Dentistry, Rochester, N. Y. Including Table of 100-Calorie Portions by Estelle E. Hawley, Esther E. Maurer and Herbert F. Van Epps, the Department of Vital Economics, University of Rochester, and Discussions of the Dietary Management in Specific Conditions. By Collaborators associated or formerly associated with The University of Rochester School of Medicine and Dentistry. With a Foreword by John P. Murlin, Ph.D., Sc.D., Professor of Physiology and Director of the Department of Vital Economics, University of Rochester. Pp. 477; illustrated. Springfield, Ill.: Charles C Thomas, 1940. Price, $5.00.

The Relativity of Reality. Reflections on the Limitations of Thought and the Genesis of the Need of Causality. (Nervous and Mental Disease Monograph No. 66.) By René Laforgue. Translated by Anne Jouard. Pp. 92. New York: Nervous and Mental Disease Monographs 1940. Price, $2.50.

The Injured Back and Its Treatment. Edited by John D. Ellis, M.D., with 7 Contributing Authors. Pp. 377; 17 illustrations. Springfield, Ill.: Charles C Thomas, 1940. Price, $5.50.

The Chinese Way in Medicine. By Edward H. Hume. Pp. 189; illustrated. Baltimore: The Johns Hopkins Press, 1940. Price, $2.25.

Progress in Medicine. A Critical Review of the Last Hundred Years. By Iago Galdston, M.D. With a Foreword by Henry E. Sigerist, M.D. Pp. 362. New York: Alfred A. Knopf, 1940. Price, $3.00.

The New International Clinics, Vol. 3, N.S. 3, 1940. Edited by George Morris Piersol, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia. Pp. 358; illustrated. Philadelphia: J. B. Lippincott Company, 1940.

The 12 "clinics" in this number are from the Cornell Medical School; the progress review is on obstetric analgesia. Of the 9 "original contributions," E. R. Long's article on pneumatocele and Auerbach's on urogenital tuberculosis attract the reader's eye.

Frank Howard Lahey. Birthday Volume, June 1, 1940. Pp. 466; illustrated. Springfield, Ill.: Charles C Thomas, 1940.

Modern Dermatology and Syphilology. By S. William Becker, M.D., Associate Professor of Dermatology and Syphilology, Kuppenheimer Foundation, University of Chicago, and Maximillian E. Obermayer, M.D., Assistant Professor of Dermatology and Syphilology, Kuppenheimer Foundation, University of Chicago. Pp. 871; 461 text illustrations and 32 full color plates. Philadelphia: J. B. Lippincott Company, 1940. Price, $12.00.

Physical Diagnosis. By WILLIAM NANCE ANDERSON, B.Sc., M.D., Associate Clinical Professor of Medicine at the University of Southern California School of Medicine, Los Angeles, California. Pp. 424; 92 illustrations. Philadelphia: Lea & Febiger, 1940. Price, $4.75.

Medical Work of the Knights Hospitallers of Saint John of Jerusalem. By EDGAR ERSKINE HUME, Lieutenant-Colonel, Medical Corps, United States Army; Knight of Honor and Devotion of the Sovereign Military Order of Malta. Foreword by His Most Eminent Highness FRA LUDOVICO CHIGI-ABANI, Prince Grand Master of the Sovereign Military Order of Malta. Preface by Lieutenant-General SIR ALDO CASTELLANI, K.C.M.G., Count of Chisimaio, Magistral Knight of the Sovereign Military Order of Malta; Professor of the Universities of Rome, London and Louisiana. Pp. 371; 130 illustrations. Baltimore: The Johns Hopkins Press, 1940.

Applied Pharmacology. By HUGH ALISTER MCGUIGAN, PH.D., M.D., F.A.C.P., Professor of Pharmacology and Therapeutics, University of Illinois, College of Medicine. Pp. 914; 35 illustrations. St. Louis: The C. V. Mosby Company, 1940. Price, $9.00.

NEW EDITIONS.

Pharmacology and Therapeutics. By ARTHUR R. CUSHNY, M.A., M.D., LL.D., F.R.S., Late Professor of Materia Medica and Pharmacology in the University of Edinburgh. Pp. 852; 66 illustrations. Twelfth Edition, thoroughly revised by C. W. EDMUNDS, A.B., M.D., Professor of Materia Medica and Therapeutics in the University of Michigan, Ann Arbor, and J. A. GUNN, M.A., M.D., D.Sc., F.R.C.P., Professor of Pharmacology and Director of the Nuffield Institute for Medical Research, University of Oxford, Oxford, England. Philadelphia: Lea & Febiger, 1940. Price, $6.50.

Recent Advances in Sex and Reproductive Physiology. By J. M. ROBSON, M.D., D.Sc. (Leeds), F.R.S.E., Lecturer in Pharmacology, University of Edinburgh. With Introduction by Professor F. A. E. CREW, M.D., D.Sc., F.R.S., Director of the Institute of Animal Genetics, Edinburgh. Pp. 329; 62 illustrations. Second Edition. Philadelphia: The Blakiston Company, 1940. Price, $5.00.

"Large sections of the book have been entirely rewritten and new chapters added on the properties of the male hormone and other androgenes, on the chemistry of the gonadic hormones, and on the methods used in the standardization of the sex hormones. Since large quan ities of the sex hormones are now available for clinical use, investigation of their actions in a variety of conditions and with adequate doses have been made and much knowledge gained of value in clinical practice." (Publication Notice.)

Heart Failure. By ARTHUR M. FISHBERG, M.D., Associate in Medicine, Mount Sinai Hospital, New York City. Pp. 829; 25 illustrations. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1940. Price, $8.50.

Practical Clinical Psychiatry. By EDWARD A. STRECKER, A.M., SC.D., M.D., Professor of Psychiatry and Chairman of the Department of Psychiatry, School of Medicine, University of Pennsylvania, etc., and FRANKLIN G. EBAUGH, A.B., M.D., Professor of Psychiatry, University of Colorado Medical School, etc. Section on Psychopathological Problems of Childhood by LEA KANNER, M.D., Associate Professor of Psychiatry, Johns Hopkins University School of Medicine. Pp. 728. Fifth Edition. Philadelphia: The Blakiston Company, 1940. Price, $5.00.

The Soldier's Heart and the Effort Syndrome. By SIR THOMAS LEWIS, C.B.E., F.R.S., M.D., D.Sc., LL.D., F.R.C.P., Physician, University College Hospital; Honorary Consulting Physician to Ministry of Pensions, etc. Pp. 103. Second Edition. London: Shaw & Sons, Ltd., 1940. Price, 8/6d.

PROGRESS
OF
MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF
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THE VULVA.

Atrophy of the Vulva. At the time of the menopause the cessation of ovarian hormonal influence is often evidenced in the vulva by certain atrophic changes. The terms kraurosis and leukoplakic vulvitis, while sometimes used interchangeably, represent different stages in these atrophic changes, while pruritus refers to the intense itching which so often accompanies these changes, although it may be due to many other causes. In a discussion of this subject, Adair, Davis and Schuitema[1] state that the physiologic atrophy of the vulvar structures predisposes to pathologic conditions. The atrophic skin is easily bruised as a result of minor trauma, coitus or infectious contacts. Repeated trauma leads to minute cracks and fissures which easily become infected by various organisms. Soon a mild infection of the skin and subcutaneous tissue is present and it is this infection which causes the symptom of itching. Constant itching leads to scratching which in turn causes more trauma to the delicate skin. This process, continued over a period of months or years, may lead to the onset of chronic atrophic dermatitis of the vulva. Three distinct stages have been described. In the initial stage the inflammatory symptoms predominate. The entire vulva is swollen, red, bruised and painful. The various structures stand out distinctly as the result of the edema which may be so marked that blebs form superficially. Petechial hemorrhages produced by the scratching give a mottled appearance to the skin. The structures are painful to the touch and a vaginal examination may provoke pain. This stage may last weeks or months but finally tends to subside and becomes subacute or chronic. The second stage is characterized by the onset of atrophic changes. The skin of the vulva becomes indurated and thickened owing to increased thickness of the keratin layer, and the usual elasticity disappears. The color may be a mottled gray with numerous reddish to pink areas where petechial hemorrhages are being slowly absorbed.

The atrophy is best seen in the region of the clitoris where the preputial folds flatten out and the clitoris gradually disappears under the atrophic hood. The entire process is definitely limited to the non-hairy portion of the vulva and is sharply demarcated at the mucocutaneous junction with the vagina but it may extend posteriorly to involve the perineum and skin posterior to the anus. The final stage is a chronic one which lasts for years. The skin over the vulva becomes smooth, glistening, semitranslucent and parchment-like and its sharp demarcation from the adjoining skin is striking. The preputial folds and clitoris completely disappear. The labia majora and minora flatten out and disappear as separate structures but may still be identified near the urethra. The vaginal orifice is narrowed and even a gentle examination causes the skin to crack and superficial petechia to develop. Pruritus is the symptom which brings the patient to the physician and it is limited to the area involved by the disease. At first the itching may be intermittent but it soon becomes constant. It does not respond to the usual antipruritic lotions and it may keep the patient awake night after night until mental and physical exhaustion develops. The progress of the disease is slow, lasting for several years and there may be periods of remission during which the pruritus subsides. The likelihood that a carcinoma will develop can be lessened only by the removal of the chronically inflamed tissue which predisposes to malignant change. The authors believe that surgical removal of the vulva is the most satisfactory treatment for patients who have marked evidences of the disease. They have found the results of surgical treatment to be excellent. The patients are usually elderly women for whom marital relations are no longer important so that introital stenosis need not be considered. Careful removal of the vulvar tissues and suitable reconstruction will leave a useful vagina when this is important. Vulvectomy carries little risk even in the old and debilitated, for it is a superficial removal of tissue and can, if thought advisable, be carried out under local anesthesia. In their clinic palliative therapy has been discontinued since no suitable local therapy has been found. It is not sufficient to allay the pruritus but all sources of irritation should be removed, which can only be accomplished by removal of the involved skin.

While there is much confusion regarding the terms kraurosis, leukoplakia and pruritus vulvæ, Montgomery, Counseller and Craig[8] state that they are usually distinguishable on clinical and pathologic grounds. In many cases all three may merge. Kraurosis is an atrophic process which may possibly lead to malignant change. Leukoplakia is a hypertrophic change, and definitely a precancerous dermatosis. Pruritus vulvæ with lichenification is a benign form of inflammatory dermatosis which *per se* does not result in malignant change. Resection of the pudendal, perineal or other nerves of the vulva is definitely contraindicated when malignant changes are either evident clinically or pathologically. In such cases vulvectomy is indicated. Resection of nerves should be avoided in the presence of psychoneurosis since even vulvectomy in these cases will be attended by many failures. Treatment with radium or Roentgen rays in cases of persistent vulvar pruritus due to any of the above conditions usually results only in temporary relief and if persisted in may lead to an actinodermatitis which may result in epithelioma of a relatively high grade of malignancy.

In the opinion of Swift,[12] leukoplakia, kraurosis, pruritus and atrophic vulvitis are due to a lack of absorption of vitamin A caused by a varying degree of achlorhydria. His experiences in Australia have shown that the addition of dilute hydrochloric acid to the normal diet of an Australian woman relieves the pruritus in the majority of cases with great improvement of the local vulvar condition. Vitamin A in the form of cod-liver oil should also be given. He feels that excision of the vulva should not be done except in those cases where there is a suspicion of malignant change.

If these changes are due to a loss of ovarian hormone it is only logical that replacement therapy with the use of follicular hormone should be tried. Rust[9] presents a summary of 65 patients with pruritus vulvæ who were treated by the use of progynon. Of this number, 48 (74%) were cured, 9 improved and in 8 patients the disease was not influenced by the treatment. Many of the patients had a severe form of the disease of long duration, in some instances of several years' standing which had resisted all other forms of treatment. If large doses of hormone are given, uterine bleeding is apt to follow as a result of hyperplasia of the endometrium caused by the hormone. This bleeding is never serious and can be controlled by reducing the dose or stopping treatment entirely. He feels that the results of this treatment are very satisfactory and preferable to such radical measures as chordotomy, nerve resection or vulvectomy.*

Foss[5] has successfully treated 8 cases of kraurosis by the injection of massive doses of follicular hormone twice weekly. After the effect is obtained a gradual reduction in the dosage must be made. He has noted a marked improvement in the macroscopic appearance of the vulva with relief of dyspareunia.

Finkler and Marks[3] have administered estrogens to 50 patients presenting symptoms of this disease. In addition to the local symptoms most of their patients presented varying degrees of vasomotor and mental disturbances. The estrogens were administered by injection, inunction of the vulvar area, by suppository or orally. The effect of the therapy was checked by bio-assays, vaginal smear and endometrial and vaginal biopsy. They have found that the selection of the type of therapy to be used varies with the individual patient, depending upon the severity of symptoms, the local condition present, whether local or general symptoms predominate and upon the coöperation of the patient. Varying degrees of improvement resulted from all four methods of administration. The greatest relief from the general symptoms was obtained from intramuscular injections, while similar relief from oral administration could be obtained if used in adequate dosage. Most of the patients were considerably helped, although failure was observed in those patients who had complicating medical conditions such as diabetes, eczema, psychoneurosis or if the local vulvar disease was extensive. Mishell and Motyloff[7] have treated senile vulvovaginitis with local applications of estrogenic ointment and obtained results that they

* The hormonal treatment is well worth trying. One of us (C. C. N.) has had marked success by employing Progynon-D H vaginal suppositories. The first suppository contains 4800 R.U. and is followed every other night with a suppository containing 480 R.U. After 11 suppositories have been employed there is usually marked improvement. The course may be repeated if necessary.

regard as striking. Estriol or trihydroxyestrin was chosen to be incorporated in the ointment base, as it has been fairly well established that this particular estrogenic substance is more easily absorbed from the gastro-intestinal tract than estrin or estradiol, and they felt that it might also be more easily absorbed through the skin. They found that the symptoms were usually relieved after 2 or 3 weeks and while recurrences may take place, they respond promptly to further treatments with the ointment. Systemic action following absorption of the hormone was evidenced by alleviation of the hot flushes so often associated with the menopause.

The treatment of pruritus by alcohol injection in 49 cases has been described by Wilson.[15] The patient is placed in the lithotomy position and the vulvar and perineal regions are prepared as they would be for surgical treatment except that shaving is not necessary. The exact areas of the vulva which are involved should be definitely marked on the skin. The patient will often point to the areas of the most intense itching and neglect to mention parts less involved. For this reason it is well to quiz the patient concerning the full extent of her annoyance, especially when the pruritus extends to the thighs, the buttocks or the abdominal wall, where characteristic changes in the skin are less prominent. The patient is then given a general anesthetic and 95% alcohol is injected by means of a 2 cc. hypodermic syringe which is calibrated in minims. The needle is inserted perpendicular to and through the skin so that the alcohol will be deposited just beneath the dermis in the subcutaneous connective tissue. An injection into the skin itself or too deeply into the subcutaneous tissues may produce a slough. Only from 2 to 4 minims of alcohol is injected at a single insertion of the needle. The number and the spacing of the injections depends on the extent of the pruritus, the age of the patient and the condition of her peripheral circulation, as well as the estimated efficiency of the circulation of the part to be injected. Elderly patients with arteriosclerosis or vulval and anal varicosities should be given injections cautiously, with a minimum of alcohol (not over 2 minims) at slightly wider intervals than younger women with efficient vascular systems. When the circulation seems unimpaired, one may inject as much as 4 minims of alcohol beneath every square centimeter of the involved skin. Immediately after the injection, the labia majora become edematous; the edema may reach its height in a few hours or perhaps in from 12 to 24 hours. After this time it slowly subsides so that after 3 to 10 days the vulva usually appears normal, though there is always a certain amount of subcutaneous induration in the region of the labia majora. This likewise subsides slowly, leaving in some cases a chain of small hard nodules, which disappear in from 4 to 6 weeks. The itching usually stops immediately, though occasionally one or two small areas of pruritus remain. These are usually areas that were overlooked or improperly treated, and they can be reinjected with the patient under local anesthesia if the itching persists after the edema subsides. As a rule this residual pruritus subsides in a few days or can be controlled with antipruritic ointments. Few patients complain of pain after alcohol injections. Although convalescence in the majority of cases amounts to little more than recovery from the anesthetic, Wilson always instructs patients to remain in bed for at least a few hours after the

injection. If the vulvar swelling becomes uncomfortable, hot moist dressings are applied. Some women resumed their usual occupation the day after injection, while others found it necessary to rest for 2 or 3 days. Wilson states that it is often surprising how rapidly the lesions heal after the injection. Excoriations, ulcerations, fissures, and so on, heal promptly and disappear in 10 days. The alcohol degenerates in the subcutaneous nerve fibers, producing a cutaneous anesthesia which persists until regeneration occurs. Probably more important are the changes in the vascular and the recticulo-endothelial system. There is a rapid mobilization of the neutrophils and histiocytes, which apparently dispose of the factors principally responsible for the pruritus as well as improving the cutaneous lesions.

Malignant Tumors. In discussing the incidence of malignancy of the vulva, Folsome[4] states that sarcoma of the vulva is rare, being either primary in the vulva or developing in the vulvar end of the round ligament. Its evolution is usually rapid, the lesion being irregular, nodular and covered with a thin layer of epidermis. It may resemble a fibroma until ulceration and infiltration take place. Once beyond local control these tumors may metastasize rapidly to most of the parenchymatous organs. Clinical experience indicates that radical vulvar surgery is the most successful treatment.* Metastatic malignant tumors of the vulva in general are rare. As to the incidence of melanoma, Folsome has found but 3 cases in his records of 39 years or 1 case to each 125,000 pelvic examinations. These tumors are usually lobulated, bluish-black pigmented tumors which grow rapidly and metastasize very early to distant organs with early invasion of the lymph nodes. While the treatment of this condition is surgical, it is important to remember that the primary growth may appear small and readily operable long after widespread metastasis has occurred. Therefore, Roentgen ray examination of the chest, a careful history and physical examination to rule out distant metastases should always be a part of the preoperative program. The prognosis is extremely poor. Carcinoma of the vulva is the most common malignant neoplasm of the external female genitalia and is primarily a tumor of senility, being seen usually in the sixth or seventh decade. The three cardinal symptoms in Folsome's experience were pruritus (58%), soreness or actual pain (48%) and spotting or irritating leukorrheal discharge (28%). If one awaits the appearance of tumor mass, ulceration or actual edema of one or both lower extremities there is little hope for a favorable prognosis. No patient with pruritus vulvæ should be treated with indifference and the presence of any small tumor or ulcer of the vulva, irrespective of the age of the patient should be removed and examined microscopically. In Folsome's clinic treatment by irradiation either with or without operation has not been very satisfactory but the type and thoroughness of the operation is the most important factor. Extensive vulvar surgery with superficial and deep bilateral inguinal resection, commonly known as the Basset technique and as advised by Taussig, gives the best results.

The late results of treatment in a series of 74 cases of leukoplakic

* In addition to radical vulvectomy and excision of the inguinal glands, Roentgen therapy is advisable.—C. C. N.

vulvitis and 112 cases of carcinoma of the vulva over a period of 30 years have been reported by Taussig.[13] He has found that leukoplakic vulvitis is permanently cured by vulvectomy in all but a few cases, although occasionally a secondary excision is required. The 5-year curability of 23 Basset operations for cancer of the vulva was 65%, while the 10-year curability was 55%. He believes that with an operability ratio of 75% and a primary mortality of only 4.6%, the surgical treatment of cancer of the vulva gives the most favorable prognosis of any form of malignancy of the genital tract except cancer of the uterine fundus. He emphasizes that radiation, vulvectomy and superficial gland operations have no place in the treatment of vulvar cancer except as palliative measures. Three out of 4 such cases should be subjected to the bilateral Basset gland excision with vulvectomy and approximately two-thirds of these will remain well for longer than 5 years.

In reporting a series of 118 cases of cancer of the vulva, Schreiner and Wehr[11] state that biopsy revealed epithelioma 115 times and adenocarcinoma 3 times. In their experience cancer may occur as a thickening of the epidermis which soon becomes cracked or fissured; as a warty or papillomatous growth which is primarily malignant; as a benign wart upon which the malignant process becomes ingrafted; or as an infiltrating type of growth which soon ulcerates, giving rise to bloody or purulent discharge or pain. As to treatment, they feel that the only hope of eradicating vulvar cancer is by its early recognition and radical destruction by coagulation plus heavily filtered irradiation. Where the disease apparently was local, 42% *lived* 5 years or more under such treatment, while 31.5% were *free from disease* for a period of 5 years or more. However, a 5-year cure is very exceptional if there is metastasis in the groins.

From his experiences with irradiation at the Memorial Hospital, Healy[6] has found that the normal tissues of the vulva will not tolerate the necessary radiation dosage. Where attempted, it has resulted in prolonged and extensive ulceration and slough, causing much destruction of normal tissues, great suffering and in many instances has probably shortened the patient's life. Attempts have been made to carry out preoperative irradiation of the lesion with radium and of the groins with Roentgen ray and, at a subsequent date, to do bilateral groin dissection and complete vulvectomy. Such attempts have been complicated by the damage resulting from irradiation and have in many instances delayed or prevented the possibility of operation. They have done a large number of complete vulvectomies at the Memorial Hospital with either single or bilateral groin dissection and have been impressed by the few cases in which enlarged palpable glands were involved by cancer, the vast majority of cases being merely inflammatory. Therefore, they have omitted radiation entirely in the treatment of the primary lesion. They do a complete vulvectomy, extending out to but not including the groins or the femoral regions. The groins are irradiated with a full dose of high voltage Roentgen ray during convalescence from the operation and thereafter are closely observed, and if any suspicious nodes make their appearance, they are exposed under local anesthesia, and radon gold filtered seeds are inserted in an amount equivalent to not less than 5 skin erythema doses to the area treated. By this procedure the primary lesion has been completely cured and

the use of interstitial radiation in the inguinal nodes not only takes care of the node but also of the surrounding gland bed.

Bartholin's Gland. In discussing tuberculosis of Bartholin's gland, Schaefer[10] states that the disease occurs as a chronic, usually non-painful, indurated swelling in which there are no signs of an acute inflammation. If the duct is patent, there may be a glairy, mucoid, brown or colorless discharge. The abscess never reaches a large size and is seldom more than 2 cm. in diameter. Incision of the gland results in a persistent draining wound. Only 8 cases, including the one which he reports, have thus far been described—all unilateral. He believes that more cases would be found if most physicians did not regard every case of Bartholinitis as gonorrheal, or if these glands were more frequently examined at operation or autopsy and if all tuberculosis institutions had a gynecologic service. It is important to demonstrate the cause of a Bartholinitis, not only to treat the gonorrhea if present, but also, if tuberculous, that other tuberculous foci, whether they be pulmonary, osseous or genito-urinary may be looked for. The most common route of infection of Bartholin's gland by tuberculosis is from a positive sputum, but it may arise from vaginal or cervical tuberculous ulcers, from the blood or lymph stream, and from the gastro-intestinal or urinary tract. The treatment of the condition consists of wide excision of the gland and its duct and closure of the wound without drainage.

Duncan[2] reports what he believes is the first case of endometrioma of Bartholin's gland. The patient complained of a hard painful mass on the left side of the vulva which had caused trouble for a year and a half. The pain became worse at each menstrual period and decreased after the flow stopped. Four years before the present admission she had had an acute inflammation of the gland, at which time it was incised and drained. The day following operation she began to menstruate. On examination, a firm bluish nodule, 2 cm. in diameter, was found at the site of the left gland and a diagnosis of endometriosis was made. The removed tumor presented the typical picture of endometriosis microscopically. Duncan believes that following the incision and drainage menstrual blood containing living endometrial cells penetrated the site of the gland and produced the tumor.

Elephantiasis. In presenting his study of 26 cases of elephantiasis of the vulva which were seen in the Charity Hospital in New Orleans, Witherspoon[16] states that this disease is a clinical and pathologic entity in which the essential pathologic change is not so much an edema from lymph stasis as a fibromatosis or hypertrophy of the underlying connective tissue. While lymph stasis is an essential step in the development of the disease and can be caused by any type of trauma or infiltration, the hypertrophic changes of the underlying connective tissue cannot occur until another factor, generally accepted as an infection of some sort, has been superimposed. The streptococcus is the commonest infecting agent, but any other organism might be responsible. The intermediate step of infection is necessary even in the type of elephantiasis caused by filariæ or other parasites. Elephantiasis of the vulva is usually caused by syphilis. The cases in this series were all in colored women, the majority of whom were in their twenties or early thirties. In nearly three-fourths of the cases clinical or serologic

syphilis could be demonstrated and in practically the same number ulceration was a factor, the portal of entry for infection thus being clear. Vulvectomy was performed on 20 cases, 2 of the remainder being poor risks, while the other 4 refused operation. A more or less complete vulvectomy was necessary in all cases. Two died, a 10% mortality, 1 from myocarditis and the other from pelvic peritonitis. Malignancy was not a factor in any case, an interesting observation, as chronic irritation is a notable feature of the disease.

Granuloma Venereum. An interesting report on the disease known as granuloma venereum (inguinale) has been presented by Wolfe and Tortora.[17] This condition is a chronic inflammatory disease of disputed venereal origin, characterized by ulcerating lesions of the skin and mucous membrane of the genito-inguinal regions and histologically by the presence of Donovan bodies in the monocytic cells of the exudate. The disease is extremely chronic and shows no tendency to spontaneous healing. It usually affects the external genitalia and perianal regions and often invades the vagina but rarely affects the cervix. The period of incubation varies from a few days to several months. There are rarely any constitutional symptoms and there is little local pain aside from burning and itching. It usually is seen in adult negroes and is thought to be transmitted by sexual contact. The lesions appear either as nodular elevations with serpiginous ulceration or as hypertrophic and keloid lesions. In the later stages secondary infection may occur and constitutional symptoms appear. Histologically, the pathognomonic cell is a relatively large monocyte 25 to 90 microns in diameter containing deeply staining bodies varying in size from 0.5 to 2 microns. The diagnosis may be difficult in spite of these characteristic cells, but the response to arsenical therapy is also helpful.

The disease is often confused with lymphogranuloma inguinale or lymphopathia venereum which is a disease of the lymphatic channels and lymph nodes, while granuloma inguinale is a disease of the skin and subcutaneous tissues. The primary lesion in lymphogranuloma inguinale is rarely encountered on the external genitalia; usually the vagina and cervix are the primary seats. The initial lesion heals quickly so that it is seldom found, while the enlargement and suppuration of the inguinal lymph nodes is frequently the first finding. In late cases a stricture of the rectum is encountered. The positive cutaneous response to injected antigen from suppurating lymph nodes (Frei test) is specific for lymphogranuloma inguinale while Donovan bodies are lacking. In the treatment of granuloma venereum Wolfe and Tortora advise tartar emetic given intravenously, beginning with 2 cc. of a 1% solution in distilled water and slowly increasing the dose until 10 cc. is reached. Injections are given every second or third day and continued weekly for 2 or 3 months after healing has occurred, in order to prevent local recurrences. Not more than 30 injections should be given in one course. Recently a new antimony drug called "fuadin" has become available and may be used intramuscularly. In rare cases where antimony is contraindicated or produces no results, surgery, Roentgen ray or coagulation must be resorted to.

Imperforate Hymen. A curious fact which has been brought out by Tompkins[14] in his excellent review of the subject of imperforate hymen with hematocolpos, is that the condition is seldom diagnosed by the

physician who first sees the case. Amenorrhea is seldom offered as a complaint. The patient's mother generally assumes that her daughter is slow in maturing and does not associate the abdominal pain which is present with failure of the menses to appear. The pain is usually poorly localized in the lower abdomen and is typically dull and intermittent rather than severe and constant. These qualities together with the history of attacks "about a month apart" often suggest recurrent appendicitis and may lead to an unnecessary laparotomy. A very common symptom is inability to void or at least difficulty in voiding. Severe pain is almost always due to overdistention of the bladder. Tompkins states that an imperforate hymen should always be suspected when an adolescent girl who has not menstruated complains of disturbance referable to the bladder. In addition to the foregoing symptoms there may be abdominal enlargement, a protruding mass at the vulva or pain on sitting. While an imperforate hymen may be found at any age, it is most commonly discovered between the ages of 11 and and 18 when obstruction to menstruation begins to produce symptoms. The diagnosis can be made at once by inspection. While several plans of treatment for this condition have been suggested, the chief complication of any of the procedures is ascending infection leading to pelvic inflammatory disease, peritonitis or death. Old blood is an excellent culture medium, and once infection enters the vagina the dilated cervix, uterus and tubes offer no resistance to its ascent. The plan of treatment which Tompkins recommends begins with meticulous preoperative preparation of the vulva and perineum. The hymen is completely excised, not simply incised and no vaginal examination is made at the time of operation. After evacuation of the retained blood from the vagina on the operating table, a careful rectal examination to determine whether there is distention of the tubes should be made. If there is evidence of hematosalpinx, laparotomy should be performed and the tubes incised and drained or, if necessary, removed. A postoperative dressing of gauze soaked in bichloride of mercury should be applied to the vulva and the patient placed in high Fowler position to promote drainage. Enough morphine should be given to produce constipation for 4 days after operation and the perineum should be carefully cleansed after every evacuation. The patient should remain in bed at least 1 week after the temperature is normal. There should be no tub bath or douching until two menstrual periods have occurred.

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REFERENCES.

(1.) **Adair, F. L.**, **Davis, M. E.**, and **Schuitema, D. M.**: J. Am. Med. Assn., **114**, 296, 1940. (2.) **Duncan, C. J.**: New England J. Med., **210**, 24, 1934. (3.) **Finkler, R. S.**, and **Marks, Z. I.**: New Jersey Med. Soc. J., **37**, 99, 1940. (4.) **Folsome, C. E.**: J. Am. Med. Assn., **114**, 1499, 1940. (5.) **Foss, G. L.**: J. Obst. and Gynec., Brit. Emp., **43**, 1091, 1936. (6.) **Healy, W. P.**: Am. J. Obst. and Gynec., **26**, 789, 1933. (7.) **Mishell, D. R.**, and **Motyloff, L.**: Ibid., **39**, 796, 1940. (8.) **Montgomery, H.**, **Counseller, V. S.**, and **Craig, W. McK.**: Arch. Derm. and Syph., **30**, 80, 1934. (9.) **Rust, W.**: Zentralbl. f. Gyn., **61**, 25, 1937. (10.) **Schaefer, G.**: Surg. Clin. North America, **20**, 459, 1940. (11.) **Schreiner, B. F.**, and **Wehr, W. H.**: Surg., Gynec. and Obst., **58**, 1021, 1934. (12.) **Swift, B. H.**: J. Obst. and Gynec., Brit. Emp., **43**, 1053, 1936. (13.) **Taussig, F. J.**: Am. J. Obst. and Gynec., **31**, 746, 1936. (14.) **Tompkins, P.**: J. Am. Med. Assn., **113**, 913, 1939. (15.) **Wilson, W. M.**: Ibid., **110**, 493, 1938. (16.) **Witherspoon, J. T.**: Am. J. Syph., **17**, 499, 1933. (17.) **Wolfe, S. A.**, and **Tortora, E. J.**: Am. J. Surg., **48**, 625, 1940.

DERMATOLOGY AND SYPHILOLOGY.

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THE PSYCHONEUROGENOUS COMPONENT OF CUTANEOUS REACTION MECHANISMS (PART II).

THE following material is the concluding portion of a review begun in October, 1939 (*Am. J. Med. Sci.*, **198**, 577). In the conclusion it is proposed to give a list of the dermatologic conditions in which psychoneurogenous components have been clearly recognized. In the compiling of such a list, it should be recalled that psychogenous and neurogenous factors may be imported incidentally into the general clinical picture of which a dermatosis is a major or minor part, as concomitants, rather than influences of etiologic importance. Thus the extraordinary seborrheic activity with accompanying dermatitis observed by Haxthausen[33a] in cases of encephalitis, is interpreted by him as a concomitant of inflammatory injury to the thalamic fat control center. The mental state of the encephalitic in general can hardly be regarded under such circumstances as of primary causative significance. Scleroderma (by which is apparently meant the acrosclerotic syndrome, rather than the morpheic type) (Sellei[60]) is by some authors rated as of neurogenic causation, because an extended literature has demonstrated the widespread nerve injuries both central and peripheral, accompanying this type of disturbance. The depressed mental state of the victim is an inescapable element in the clinical whole, but it is a question whether the psychic factors involved play a primary or a secondary rôle. In the clinical observation of such patients, psyche and soma often seem rather to be involved in a vicious circle, in which physical malfunction leads to depression and depression in its turn to even more exaggerated physical malfunction. The question also arises as to just where one should place the trophoneurodermatoses such as the chronic unilateral dermatitis of the face described by Becker,[7a] Herrick,[34] Netherton[49] and others (*cf.* Loveman[45]), as an accompaniment of gasserian ganglion extirpation or destruction. Zosteriform eruptions associated with infective injury or malignant cell infiltration of cranial or spinal nerve sensory ganglia are neurogenic perhaps in much the same sense.

The multiplicity of causes which characterize the mechanisms operating in the production of many skin diseases also obstructs listing. The interaction of emotional and allergic factors and the infection-

allergic complexes alone greatly increase the difficulty of giving an exact rating to the psychoneurogenous in the eczema-asthma-hay fever complex (prurigo Besnier); in dyshidrosis (infective-allergic conditions of the hands and feet); rosacea and the "flush" dermatoses and so forth. The interplay between infection and contact allergy on the one side, and the nervous control of perspiration and circulation on the other, make it extremely difficult to decide at what point the seemingly vicious circle begins or ends. It is clear, then, that classification will probably be even more difficult than listing.

Rogerson,[66b] in listing the dermatoses in which the psychologic factor can be recognized, places erythema, dermographism, urticaria, eczema, pruritus, prurigo (Besnier) (the eczema-asthma-hay fever complex), alopecia areata, vitiligo, scleroderma, dyshidrosis and neurotic excoriations (self-inflicted eruptions) in his major classification, and places herpes simplex, lichen planus and psoriasis in a group in which emotional disturbances are only occasionally seen to be of etiologic importance.

Becker,[7b] from a study of the physical and mental backgrounds of patients with neurovascular instability, as he designates it, lists the following as functional dermatoses which may properly be spoken of as "neurodermatoses"; idiopathic pruritus, generalized and localized; neurotic excoriations, neurodermatitis (dry and exudative types), dyshidrosis, idiopathic chronic urticaria, and angioneurotic edema, alopecia areata, totalis and universalis, lichen planus, vitiligo, rosacea.

The following is a discussion based on attempted classification.

Disorders Affecting Hair and Pigment (alopecia totalis, alopecia areata, vitiligo, pigment anomalies, trichotillomania). Beeson and Pickett[8] have furnished the most recent summary in the American literature on the causative background of geographic and total hair-loss, based primarily upon repetition of the experimental work of Max Joseph.[38] Genner,[25] 4 years earlier, admirably summarized current clinical knowledge in a monograph on pelade in which he classified alopecias of the island type into three groups: the first due to peripheral nerve injury, especially in the neck; the second due to general disease of the nervous system; and the third to emotional shock. The experimental work on cats performed by Joseph and repeated by Beeson and Pickett, with alopecia developing at varying intervals following nerve resection in approximately 33% of cases has been subjected to a thorough-going control critique by Aubrun.[4] By covering with a leather cap the areas about the heads of his cats, in which "alopecia" and "trophic" lesions usually developed, Aubrun was apparently able to show that "neurogenic" alopecia may be an artefact produced by the cats' scratching of itching and hyperasthetic areas. The traumatic factor apparently looms large in what had previously been accepted as an experimental demonstration of true trophoneurotic origin. Wright,[67] as the result of cervical plexus resection in man, could find no evidence for the trophoneurotic origin of alopecia areata. Over against this inconclusive experimental material must be set a gradually increasing accumulation of individual cases in man, in which nervous shock has been followed by total or partial hair-loss. Wright has suggested as the result of his negative experiences in the experimental field, that the underlying mechanism of alopecia areata is vasomotor or circulatory rather than neurogenic,

as such. The suggested instrumentality of endocrine disturbance rests on such slender evidence as hair-loss or hair-growth conditioned by pregnancy or associated with thyroid disturbances.

The association between hair-loss and hair-depigmentation is clinically familiar. Genner,[25] Brown[16] and Roxburgh[57] believe that there may be neurogenic factors in vitiligo. Ramel,[53] in a rather loosely hung discussion, includes both depigmentation and hyperpigmentation among these trophoneuroses. Klauder,[42a] examining the question of sudden loss of hair and sudden turning white of the hair, finds many of the cases to be apochryphal and the most recent credible account to be that of Vignolo-Lutati[64] (1918) in connection with war shock and so forth. Goodman[29] has made the interesting suggestion that the pattern baldness over the temples and that over the tonsure area has a distinct trophoneurotic background, dependent on the age of the individual. He points out that in the preadolescent, thallium acetate produces a hair-fall over the entire scalp, whereas in the adult only the hair of the tonsural area falls.

Trichotillomania is not a trophoneurosis, but a habit spasm or tic, with a definite psychogenous background. The pulling out of the hair and the breaking off of hairs (trichokyptomania) produces patterns easily confused with other geographic types of alopecia, and the nervous tension and conflict developed by parental repressive influences, school stresses, hysteria and compulsion neurosis are usually not apparent until several consultations have been had. Most of the victims are adolescents, and Klauder credits mass suggestion that epidemics of the disturbance observed in boarding schools and so forth are due to mass hysteria. Alkiewicz[1] has reported a case of picking off of the nails, which evidently belongs in the same group of conditions.

The Self-inflicted Lesions of the Skin (factitial dermatoses, dermatitis artefacta). The more or less standard presentations of this subject including those of MacKee[47] and Stokes and Garner[61f] have been supplemented since 1929 by analyses of individual cases emphasizing psychical factors, such as that of Gillespie;[26a] Saegesser's[59] very interesting discussion of leg ulcers in which it appears that a psychic stigmatization factor necessitating attention to the mental state of the patient is operative; and Rogerson's[56b] case suggesting that occupational contacts and neurogenic factors may be interwoven in the background. Gillespie emphasizes the diagnostic importance in identifying the hysteria factor in self-inflicted dermatoses, of the appearance of hysterial paralyses. He differentiates the true hysterical cases from the more commonplace examples of malingering, attention-getting and similar motivations. He believes that hysterics in general may not know *why* they produce signs and symptoms of illness, but that many more are aware that they do actually produce them than is commonly believed. The patient thus inflicts the lesion in full consciousness of everything but the motive back of the act. Gillespie even believes that the amnesia with respect to motives may be an artefact and the result of self-deception afterwards, the patient lying in self-defense and then coming to believe his own tergiversation. The domination by a fixed idea may proceed to the point of permitting amputation, though the amputation is not proof positive of hysterical origin, and may occur as part of a compulsion neurosis.

Haxthausen concludes that hysterical lesions of the skin are purely of external traumatic origin, and belong to the group appropriately labeled "pathomimia." He finds no evidence that the skin of hysterical individuals reacts with abnormal severity towards external irritation; but Bettmann,[9] Rasch[54] and other older writers maintain the contrary. Haxthausen,[33b] by a series of experimental studies, apparently demonstrated that there is no intrinsic difference between the reactivity to trauma of hysterical and normal skin, though he concedes that the attempt at evaluation of the experimental trauma may be conditioned by the hyper- or hyp-esthesia frequently noted in hysterics.

MacCormac's[46] recent presentation of so-called "autophytic dermatitis" gives a useful classification into: 1, *purposeless hysterical eruptions*, almost exclusively confined to young unmarried women; 2, *Purposeful and hysterical eruptions*, occurring in women of mature age who attempt to evade unwelcome duties. This is the malingering group in which monetary or other gains, or the avoidance of disagreeable duties is obvious; 3, *the mischief group* in which children desire to mystify their elders; and 4, *phan'om dermatosis*, in which the patient complains of a dermatologic condition which he considers obvious and disfiguring but of which no traces can be found by an unprejudiced observer. MacCormac gives an interesting prognostic note regarding 11 young women followed over a period of years, all but 1 of whom ceased to inflict lesions on the skin and entirely forgot their previously conscious acts.

Gillespie gives the most recent classification of motives in self-inflicted skin lesions as follows: 1, dermatitis artefacta as a "dodging reaction," for the avoidance of some difficulty; 2, as an attention-getting device; 3, as part of an hysterical syndrome; 4, as a symptom of a compulsion psychoneurosis; 5, as a mode of exhibitionism. Cases illustrating each type are given. Gossip,[30] in discussing vicarious menstruation, points out its relation to hystero-epilepsy. He believes that the hysterical factor outweighs ovarian endocrine influences, prepuberal maladjustments and menstrual irregularities. Brown,[14] in presenting what he believes is the first case of dermatitis artefacta treated by psychoanalysis, quotes Prosser-Thomas[52] as calling particular attention to the favorable significance of anxiety and depression developing in the hysteric as he becomes aware of the nature of his acts of self-infliction. Brown's psychoanalysis of his patient, which resulted in the permanent cure of the patient's ulcers, attached the mental process to a masturbation episode and masochistic scratches. Saegesser's[59] very interesting study of leg ulcers in a young woman gives a number of reasons for his belief that her introspective contemplation of the ulcer and its intimate association with unhappy episodes was a factor in maintaining the pathologic condition which was only overcome by distracting her attention from the lesion, and concealing it from sight. Apparently no outright self-infliction was involved. Rogerson's[56b] case, combining occupational and neurogenous factors, occurred in a worker who developed a cement dermatitis of the hands which improved but did not clear on occlusive dressings and elimination of the occupational factor. The anxiety element was conspicuous until a complete change in his psychologic outlook took place with the awarding of adequate compensation. Thereupon the dermatitis disappeared. Cases such as these,

if a sufficient number accumulates, will tend to support via the vasomotor mechanism in all probability, the belief supported by Klauder[42b] in his discussion of stigmatization, that psychic processes are able to affect the localization as well as the severity of cutaneous lesions.

Erythema-Urticaria Group (including vasomotor neuroses). Under this title there are included by various authors the cutaneous edema phenomena of dermographism, urticaria and angioneurotic edema, conditions associated with angiospasm, including Raynaud's disease, acrosclerosis and scleroderma, the "flush" dermatoses, including rosacea and erythromelalgia; and hemorrhagic (stigmatization) phenomena. In connection with the urticarias especially, mention has already been made of the cholinergic type whose mechanism is described in the previous review. Urticaria associated with sexual relations is not unfamiliar and Dunbar[21] has rather startlingly analyzed a case in which a young woman spontaneously developed urticaria as a method of compromise, so to speak, between the desire of her sadistic partner to raise welts on her with a belt, and her feeling that she should dismiss him, though she ardently desired to retain his attentions. By raising her own "welts," she retained her partner and avoided the beating. When the mechanism was explained the urticaria disappeared. Stokes, Kulchar and Pillsbury[61g] give some rather interesting figures as to the importance of the psychoneurogenous factor in the multiple etiology of chronic urticaria. A psychoneurogenous factor was present, plus other causes in 68% of cases. Psychoneurogenous factors were the sole recognizable cause in 12% of cases, and no psychoneurogenous factor could be recognized in 17% of cases. Nine cases are cited with various types of precipitating incidents and response to a psychic reëducation technique. Urticariogenic response seems to have familial or even hereditary background, and to be based on what Stokes[61c] subsequently called the "tension frame of mind." Rogerson[56a] adds to the accumulating evidence that urticaria produced by physical allergens can be influenced by psychic factors, the case of a boy allergic to fish and Brazil nuts whose allergic symptoms disappeared when in a happy frame of mind.

Rosacea and congestive conditions of the flush areas were connected with the psychogenous influence of the slow-acting long-time chronic wear-and-tear type by Stokes and Beerman.[61e] The very important influence of guilt and anxiety, summarized by Klaber and Wittkower[41] under the term "social anxiety" in the etiologic background of rosacea, has recently been strongly supported by their special studies. The flushing of the center face, on which develop acneiform eruptions, exaggerated seborrheic processes and so forth, was in 36 of their 50 cases apparently the direct result of acute psychologic trauma, and in a further 20 cases, of a preceding prolonged social or sexual stress. The vascular congestive base of the process is linked with Harmer and Harris'[31] observations on the similarity of the rosacea syndrome to that induced by the injection of histamine. This possibility is also invoked by Stokes and Beerman, the histamine-like substances being absorbed as the result of gastro-intestinal abnormalities developing in the rosacea type of patient.

The Angioneuroses, Angiospasm, Erythromelalgia. Surprisingly little attention has been given in recent years to the psychoneurogenous background of the vasomotor neuroses. Vorhees[65] pointed out the effect

of worry, excitement in producing paroxysms, and the influence of nervous states on "dead finger," acrocyanosis and so forth, seems tacitly accepted without an adequate analytical study. Erythromelalgia has had practically no critical examination from the standpoint of psychoneurogenous factors in even such an extended report as that of G. E. Brown[15] from the experience of The Mayo Clinic. This silence on the matter is the more interesting in the light of the report of Mumford on a case of monolateral erythromelalgia, apparently of hysterical origin, cured by suggestion. The observations of Hartson[32] on so-called stocking erythrodermia afford interesting linkage between the pure vasomotor neuroses of the extremities and those vasomotor disturbances which underlie the development of actual dermatitis of the hands, legs and feet. O'Donovon[50] deserves credit for insistent emphasis on the importance of psychoneurogenous factors in conditions of this sort.

Vagus-Sympathetic Imbalance. Brill's[13] observations on the preponderantly vagotonic background of the neurodermitides, have been followed by Rogerson's endorsement of the importance of vagus-sympathetic imbalance with emphasis on the vagotonic type of disturbance, as characteristic of prurigo (Besnier) and the eczema-asthma-hay fever complex. Rogerson[56b] requotes, as worthy of extended emphasis, the clinical characteristics both of the skin and other structural systems, predicated by Eppinger and Hess,[24] for the vagotonic and sympathicotonic types.

The Vagotonic Type.

A. Exemplified by the person with the asthma-eczema-prurigo syndrome.

B. Psychologically usually introvert.

C. Cutaneous characteristics: complexion sallow with an earthy tint; lips bluish; skin appears thickened and harsh; tends to be edematous owing to the retention of fluid in it: marked tendency to hyperpigmentation, particularly in the areas of the prurigo; white dermographism; scratching and rubbing result in lichenification; hyperhidrosis of the extremities may be present, but skin as a whole is dry and often ichthyotic. Response to anger: pallor.

D. Vascular system: blood pressure tends to be low, particularly when exhaustion of the adrenal sympathetic system occurs after nerve strain or acute infection; with fall of blood pressure increased pigmentation is likely to appear. There is often circulatory stasis in the extremities so that hands are bluish and cold to touch. Erythrocyanosis of the legs is common in females. Capillaries fill slowly after obliteration by pressure. Pulse rate tends to be slow and temperature to be subnormal.

E. Tolerance to adrenalin and thyroid extract high.

The Hypersympathicotonic Type.

A. Exemplified by the person with established or potential Graves' disdisease.

B. Psychologically usually extrovert.

C. Cutaneous characteristics: skin usually white, thin and transparent, with marked tendency to flushing (erythema); lips bright red; vitiligo rather than diffuse pigmentation common; also alopecia areata and scleroderma; red dermographism often with whealing; lichenification rare; generalized hyperhidrosis common. Response to anger: flushing.

D. Vascular system: blood pressure likely to fluctuate, temporarily high in states of emotion and excitement. Peripheral circulation usually good and extremities warm but Raynaud's disease may occur. Capillaries fill quickly after obliteration by pressure. Pulse rate tends to be rapid, and the heart beat tumultuous. Temperature is normal and may be raised in state of emotion.

E. Tolerance to adrenalin and thyroid extract low.

Szondi[63] and, more recently, Becker have pointed out that pure cutaneous vagotonia and hypersympathicotonia rarely exist, and that both are essentially structural or local neural disturbances, so that a hypersympathicotonic skin may be accompanied by vagotonic gastro-intestinal tract and so forth. Becker has developed the term "neurocirculatory instability," as covering both types of conditions, and as descriptive of the type of patient who tends to develop the dermatoneuroses. It is at once apparent to students of this problem that the proportion of psychoneurogenous influence in all of these conditions varies not only quantitatively, but qualitatively, and that it is therefore hazardous to propose outright an inclusive list of neurodermatoses, and preferable to speak of the psychoneurogenous components in this, that, or the other dermatosis.

The Besnier prurigo or eczema of the eczema-asthma-hay fever complex, conforms in clinical experience so closely to the vagotonic type of cutaneous disturbance and has such distinct entity characteristics, that the work of the Gillespie-Guy's Hospital group including Rogerson and Strauss, on the psychogenous background of the eczema-asthma-hay fever complex should be summarized here:

Based upon Rogerson's[56] studies of the material of the asthma clinic of Guy's Hospital and the observations of Stokes[61d] and others on the adult personality, the psychologic background of the eczema-asthma-hay fever complex may be summarized as follows:

1. A deep-seated feeling of insecurity.
2. An easily developed feeling of inferiority.
3. Aggressiveness; disposition to dominate, demand attention; a species of drive, possibly compensatory for (1) and (2), but also including an element of—
4. An intense self-consciousness, or I-sensitiveness, the "Liebe Ich" or "Beloved I" of the German literature. This is less a vulgar and robust egotism than it is a kind of ultrasensitiveness, like hypersensitiveness to physical pain.
5. Marked lability of physical and mental reactions, which in some becomes adaptability and in others instability.
6. An intrinsic kinetic drive, a species of thalamic pressure, which is probably interwoven with or causative of (3) and which is at the bottom of—
7. An all-or-none type of reactivity, a species of spark-over which knows no half-way or compromise approaches to problems, or reactions to stimuli (with spasmophilia as a physical expression?), plus—
8. A higher-than-average intelligence quotient, plus—
9. Tension, expressed or repressed.
10. A restlessness which is not instability, but is due to the rapid exploration and exhaustion of a subject, a problem or a possibility by a high-pressure mind of exceptional capacity. The constant exhaustion of the possibilities of the moment or the situation, leads to boredom and flight rather than exhaustion and rest.
11. A deep-seated over-dependence, product of (1) and (2) with traces of (3) and (4).
12. A special reactiveness to competition, human and personal, possibly a product of (1), (3) and (4).

The work of Rogerson and Strauss[56c] in clearing the Southampton Asthma Retreat of Guy's Hospital of patients who now largely carry on in complete freedom or greatly improved status at home, through the application of psychotherapy directed at the above-described background, is the best testimony available to the significance of the psychologic element in this group of cutaneous conditions.

Inflammation (dermatitis and eczema). It is again fundamentally necessary in reviewing psychoneurogenous components in inflammatory disease of the skin, to keep constantly before one the etiologic complexity underlying regional and general dermatitic eruptions. Where the causative mechanism may and constantly does involve elements of insufficient or disturbed physiologic defense (ichthyosis, seborrhea); various forms of allergic disturbance due to inhalant, ingestant and contact agents; various infective elements (fungi, pyogens especially); light sensitiveness due to local or systemic conditions, it must be clear that the psychoneurogenous element, operating as it probably does, largely through vasomotor and sweat disturbances quite apart from any supposed distinctive "trophoneurotic" mechanism, must be very conservatively interpreted in order to avoid the grossest forms of "*post hoc*-ism." One of the best series of case descriptions evidently involving psychoneurogenous factors without necessarily a clear-cut placement of this element in the etiologic complex, is that of Klauder. This presentation is typical of a number in the literature in which the psychoneurogenous factor in the background is clearly present, but the instrumentality through which it operates is either not completely investigated, or is otherwise not adequately defined. Much of the available information in the literature is in precisely this state of inadequate definition. Here and there individual items, particularly involving the allergic state, have been clarified by responses or cures obtained under hypnosis or illuminated by experimental studies such as those of Diehl and Heinichen,[20] but the relative proportion of established and presumed connection is still much too large on the presumptive side. In the case of neurodermatitis and the flexural eczemas, interesting connections with such phenomena as histamine intoxication are developing. It is clear that histamine intoxication is accompanied by a mental state comparable to that of the depression of many neurodermitics; and similarly it is clear that histamine when injected intramuscularly can give rise to an increased skin temperature conforming in distribution characteristics to the clinical picture of neurodermatitis (Williams[66]). Reference has already been made to the emotionally controlled apocrine sweat mechanism, and its relation to flexural mycoses and streptomycoses (Darier-Ravaut-Ramel syndrome[55]). The so-called dyshidroses (dermatitic or eczematoid eruptions of the hands) probably provide at this moment the clearest illustration of the importance of psychogenic factors in the complex of allergic-infective dermatitis that we have available. Hartson, mentioned above, as long ago as 1929 reported a series of so-called stocking erythrodermias, of which O'Donovon also had cited cases which he regarded as a clinical entity in which he believes the psychogenic factor was so important as to justify classification with the neurodermitides. Treatment in these cases, however, suggests that such factors as mild venous stasis had not too fully been considered. Becker cites several case histories, in

which the etiologic work-up however can scarcely be regarded as complete. The approaches from the psychiatric side have also not taken too seriously the necessity for a comprehensive etiologic study in these cases. Bartemeier's[6] review of the literature including the cases of Jelliffe and Evans[37] (psoriasis as an hysterical conversion symbolization), Allendy[2] (eczema of the hands), Barinbaum[5] (eczema of the fingers, 1 case; inguinal intertrigo, 1 case) all appeared to lack comprehensive study from the standpoint of infection-allergic factors, among others. Bartemeier's own case of a 25-year-old Jewish dental student with a patch of dermatitis on the dorsa of the hands, cured with 2 years' complete freedom from relapse, by psychoanalysis, approaches more nearly at least a demonstration of the influence of the psychogenic in these cases.

Barber, the head of the Dermatological Clinic at Guy's Hospital, and Gillespie (case reported by the latter) described a case in which they believed that the use of the hands in the occupation is what determines the expression of dissatisfaction by a skin lesion of the hands, rather than some other organ. This is particularly discussed as significant in certain types of occupational dermatitis (Rogerson's case of cement worker already referred to). Kelman and Field[40] describe a case which illustrates quite strikingly the succession of contact and other allergic accidents, intercurrent infective predisposing elements and so forth, which may interact with the psychogenous background of certain types of patients. An even better case is that reported by Pearson[51] of dyshidrotic eruption of the hands and feet cured by psychoanalysis and psychotherapy after the complete failure of thoroughgoing and careful topical and systemic treatment for the allergic-infective elements. This patient, who suffered immediate exacerbation of her eruption under even such relatively minor stimuli as waiting in the office, was found to be the victim of a conflict similar to that which was responsible for Gillespie's[26b] case of excessive sweating. Adjustment of the conflict led to a complete and lasting recovery.

Trophoneuroses. It is proposed here only to mention such cases as that of Becker's woman patient with unilateral dermatitis of the face, and gingivitis, developing after the removal of the gasserian ganglion. The literature includes besides the older cases, recent reports by Herrick,[34] Netherton,[49] and Loveman.[45] The instrumentality of the Lewis-Dale or antidromic nerve impulse mechanism deserves consideration here.

Disorders of the Sweat Mechanism. Dermatoses ascribable to abnormality in the nervous control of sweat were discussed in as great detail as the literature permits in the preceding section of this review. It should be recalled that the apocrine sweat glands are known to secrete odoriferous substances which may be responsible for bromidrosis, but the complexity of the bromidrosis problem is well illustrated by a recent summary (*J. Am. Med. Assn.*, **112**, 1408, 1939).

Pruritus. The recent physiology of the itch mechanism is dealt with in the preceding section of this review. The current neuropsychiatric contributions concern mainly the sex or erotic elements in pruritus. Generalized itching associated with extensive dermatitis or eczema, and with neurodermatitis, and pruritus without obvious cutaneous lesions

have been described with attendant circumstances suggesting masochism and cutaneous masturbation by several authors including Stokes.[61a] Klauder has on various occasions expressed the belief that such relations can be overemphasized. Rogerson's recent review, however, cites in detail Cormia and Slight's[19b] case, which seems inescapably one of scratch substitution in an unsatisfactory sexual relationship. Gillespie described a case of general prurigo with severe cutaneous masturbation accompaniment. *Pruritus ani et vulvæ* seem to be more clearly recognized as having sexual components. Hunt,[35] however, in 300 cases of pruritus vulvæ, thought that only 8 presented incontestable evidence of the psychogenous cause, operating alone, although in many other cases psychogenous factors were identifiable. Rogerson, in discussing this question, emphasizes that sexual factors may appear in married quite as often as single women, that they may be expressions of sexual tension, and that the eczematous manifestations accompanying the pruritus may be utilized as a method of avoiding normal relations. This is also true in the case of excoriation produced by scratching. Gillespie's case illustrates the succession of needless operative and other interventions to which the sexually grounded pruritus vulvæ may be subjected. Symptoms disappeared when this patient was released from parental domination, especially that of the mother, and her anxiety about her sexual problems was relieved. Kreis[43] reports 4 cases of pruritus vulvæ successfully treated by psychoanalysis.

Pruritus ani seems to be a more tempting field for psychosomatic explanations even than pruritus vulvæ. Gillespie's case illustrates the combination with exhibitionism. Gillespie points out that giving anal anesthetics to children may encourage what is almost a normal anal eroticism in the early years of life. He also points out that the most commonly produced lesion, lichenification resulting from scratching, requires not only the surgical or other treatment usually accorded it, but treatment of the sexual neurosis underlying the pruritus. Rogerson says that pruritus ani may also give a clue to the existence of unsatisfied homosexual desires, and that in these circumstances, the use of local applications is apt to be harmful rather than beneficial. Stokes,[61d] in a discussion of the treatment of pruritus ani, includes the anal fixation mechanism and anal eroticism among the factors in refractory cases. One of the cases he describes illustrates the concomitant occurrence of itching and lichenification of the posterior scrotal wall as an expression of sexual tension in the male. Gillespie, in his general discussion of pruritus, makes a significant correlation between the worrying depressive type of personality, which expresses uneasiness of mind by uneasiness of skin (itching) with associated scratching. He says, "The skin is chosen as a means of expressing anxiety of a general kind; although it is possible that it is so chosen because scratching acts as a temporary means of allaying the physical uneasiness produced by uneasiness of mind," just as some people take to masturbation when they are worried. This suggested relationship probably has an important bearing on the cutaneous scratch activities of the EAHF (eczema-asthma-hay fever) type of person, as brought out by Stokes.[61b]

Topalgias and Phobias. The topalgias, or localized pains in the skin and mucous membranes have been extensively discussed by Klaudre,

Gillespie, Kelman and Field. The original observations of Blocq[12] have been fully confirmed. Gillespie points out that the self-infliction of pain through the skin may be determined primarily through a sense of guilt. The skin may also be subjected to manipulation responsible for or secondary to skin pain, under the influence of exhibitionistic tendencies. Klauder gives 2 cases, 1 of dermatothalasia, produced by an intolerable local pruritus, and a second patient, who had insight into the psychologic mechanism of his skin symptoms and his traumatizing reactions to them which he used as a method of escape.

Klauder, in commenting on "burning tongue" which has been admirably described by Montgomery,[48] states that in his experience the symptom is invariably an expression of fear of cancer, often aroused by suggestions from various sources, including indiscreet remarks of physicians.

The dermatophobias include most conspicuously fear of hypertrichosis, which can develop into a severe form of obsession through a wide variety of shocks and tension-inducing circumstances. Peladophobia, fear of baldness, occurs more frequently in women than is realized. Acarophobia, or fear of parasites, can frequently run in epidemic form through a family or group of people as the result of an indiscreet remark or therapeutic overactivity on the part of a physician.

Miscellaneous Non-classifiable Dermatoses—*Psoriasis.* Bunnemann,[17] who is largely responsible for the conception of "shock psoriasis," describes a case in which psoriasis apparently developed following trench experiences, disappeared following suggestion under hypnosis which did away with the effects of the trench impressions, and recurred again after suggestion under hypnosis had reëstablished the original neurotic basis. Goldsmith described a case in which a profuse psoriatic eruption preceded a dreaded operation. Becker and Obermayer[7c] confirmed for their experience the rather general impression that generalization and flare-ups of psoriasis can be brought on by tension factors similar to those underlying the neurodermatoses.

Lichen Planus. Goldsmith,[28] in reviewing the literature of lichen planus, gives as opinion rather than as demonstrated fact, the view of a number of dermatologists who feel that there is a strong psychoneurogenous background in lichen planus. To these views he does not in the main, himself, subscribe. Kartamischew,[39] whose exploits with hypnosis certainly need confirmatory study, caused the eruption of lichen planus to disappear in 3 out of 4 cases, by psychotherapy. Sack[58] secured a recovery in a woman physician by psychoanalysis. Eller[23] reports cases following the stock-market crash which recurred under subsequent tension disturbances. Goeckermann[27] reports a resistant lichen planus which presently subsided readily without further treatment when financial worries were adjusted.

Warts. The response of a filterable virus infection to suggestion invariably is received with surprise and incredulity by the medical mind. The original and carefully controlled work by which the psychotherapeutic factor was conclusively demonstrated was done by Bloch[11] at the inspiration of Heim, the geologist at the University of Zurich, who, like his father, was widely known as a wart-curer. Many interesting sidelights on Bloch's experiences are included in the discussion

by Sulzberger and Wolf[82] of this work. The cure of a skeptical neuropsychiatrist is included among the cases there described. Bloch's percentage of successes was 44 for verruca vulgaris, and 88.4 for verruca plana juvenilis. Assistants of lesser prestige and convincing capacity with the method, obtained serially lower percentages (44, 35, 31, 25). One clinic patient, who could not be cured, responded promptly in Bloch's private practice. It is impossible here to give a full account of the many remarkable and interesting features of this really courageous piece of work. Studies in this country have reasonably confirmed the conclusion that at least a 50% proportion of the effect of any mode of treatment of warts may be attributable to suggestion. Allington[3] succeeded in showing under adequate control that colored distilled water was as effective as sulpharsphenamine when neither patient nor physician knew which was used. The contrast between Biberstein's[10] success with a wart "vaccine" and Cormia's[19a] failure by identical methods seems very probably due to suggestion; the former author having confidence in his method, and Cormia using it after deliberately depreciating the procedure as much as possible to the patient who was about to receive it.

The General Psychotherapy of Psychoneurogenous Components in Skin Diseases. The disposition of dermatologists to depreciate the psychogenous element in dealing with cutaneous disease has delayed materially the development of rational psychotherapy. If a clear-cut psychogenous element is recognizable, a psychiatrist may be called, but the large proportion of patients, especially those presenting the eczema-asthma-hay fever complex and the conditions influenced by the "tension frame of mind" can neither afford nor will accept extended psychiatric treatment for what they regard as the ordinary problems of human worry. Attempts have been made to place the relatively commonplace psychotherapy indicated on an accessible basis usable both by general practitioners and specialists interested in this sort of work. Useful contributions in English have been those of the Gillespie group, headed by Drake, Rogerson and Strauss at Guy's Hospital; Becker and his associates at the University of Chicago; and Stokes and his associates. Becker's various contributions recently summarized emphasize the necessity for controlling the environmental factors after an extended inquiry into the whole situation involving the family, occupation, the patient and so forth; treatment of the nervous exhaustion factor. Becker particularly emphasizes the value of reassurance, rest, including vacation, retirement and heliotherapy. Sedation with drugs occupies a varying place and is employed by Becker, usually as phenobarbital and calcium. Local treatment is regarded chiefly as palliative. Stokes and Rogerson have written in fairly close agreement on the eczema-asthma-hay fever type. In the former's account of an office technique of psychotherapy, the process of estimation of the patient's personality; landmarks in the recognition of tension; an appraisal of the vasomotor sweat and gastro-intestinal mechanisms are described. He then proceeds to the establishment of rapport, lists the commoner nervous factors; gives an office technique for catharis and the confessional approach, and designates under eleven heads the elements or insight leads which are to be looked for in the patient's state of mind. Active treatment

begins with reassurance and readjustment, following sixteen points in a defined schedule; a technique for securing complete rest, including tension release and tension discharge; the former following closely the relaxation physiology of Jacobson.[36] The views and experience of Rogerson and Stokes are combined in two recent tabular summaries, the Rogerson contribution being taken from the Practitioner (1939)[56b] and from personal exchanges. The second summary deals specifically with the tension frame of mind which underlies such dermatoses as urticaria, rosacea and so forth.

Basic Psychotherapy of the Eczema-Asthma-Hay Fever Patient. I. For the Infant and Prepuberal Child. 1. Supervised play with other children under child guidance and nursery school direction.

2. Calling off of the oversolicitous and overprotective parent.

3. Treatment of the child as an equal, with explanation, patience, *laissez faire* and persuasion replacing to varying degrees parental sovereignty, severity, repression, irritability and don'ting.

4. Elimination of as many contacts as possible with the irritating ("electric") or irritable and repressive parent or other personality (school, away from home, etc.).

5. Adjustment of marital and personality conflicts between parents and insecurity-producing discriminations among children in the family as promptly and as early in life (even prenatally) as possible.

6. Discouragement of the forcing tactics, marks standards and competitive techniques of teachers, schools and sports.

7. An attempt to conserve rest—not too many visitors, not too much excitement, the midday quiet period if not nap, combating of night life, overstudy, and so on.

8. Facilities for tension discharge, non-competitive sport and exercise, *outdoor* life, nature study. The EAHF is a radically different being in the open.

9. Training in self-confidence and self-reliance—exploration, experiment, trips alone, direct relations with teachers, advisers and physicians, not mediated through the parent. Systematic but not exaggerated encouragement.

II. For the Adult EAHF. 1. Not too much explanation of the mechanism which characterizes or creates the mental state—at least not to the more unstable subjects.

2. An attempt in suitable cases to manage the parent problem as in the child, but more circumspectly.

3. An effort to identify in simple conversations on current activities of the patient, his plans and problems, the more obvious conflict factors, and especially the critical inferiorities, which in crisis form can precipitate asthmatic and neurodermitic explosions.

4. Education as to I-sensitiveness, kinetic drive, effect of competition, in one or two simple talks.

5. Systematic encouragement combined with emphasis on self-acceptance and de-personalization of outlook.

6. An arbitary rest prescription with reduction in scholastic, extracurricular, sport and social tension activities by 35 to 50% until improvement takes place. Permanent reductions in scale of attempted activity and achievement.

7. Training in a technique of relaxation.

8. Training in tension discharge via the long muscles—especially walking (cross-country preferred) from 1 to 4 hours daily, mind on the present, without thought of past or future and without time schedule or destination. This is to be supplemented by a manual hobby and an outdoor non-competitive sport (rowing, canoeing, swimming, sailing, skiing, skating, etc.). *Not* driving a car, which is a "poisonous joy" for these people.

9. Change of scene (*i. e.*, adjustment by flight) only in critical and unmanageable situations.

Basic Psychotherapy of the Tension Personality. 1. A talk on general principles in which the fundamental nature of tension is explained, with its relation to skin behavior.

2. The attack on the obligatory in repeated sessions by (*a*) the injunction *not to do* whatever gives the patient a feeling that it *must be done.*

3. Cutting off access of the "*must*" influences to the patient—severe cases no mail, no answering of telephone, no making or meeting of engagements, no acceptance of new, and a repudiation of up to 50% of current social commitments.

4. Provision of *physical sanctuary* (own work-room, garden, etc.) to be used for set period each day.

5. A lecture on "don't give a damn"—the "DGAD" or temporarily conscienceless attitude, illuminated by slogans of "a hundred years from now—" and so forth.

6. Drill in relaxation, both systematized as "exercises" and in waiting with patience (doctors' offices, traffic lights), substituting shrugs for jaw-clenching and nail-gnawing.

7. Provision for tension discharge by non-competitive physical, means (*notably* again *walking*) and manual hobbies. Stopping competitive sport and "exercise."

8. An arbitrary rest prescription based on the above elements—usually 1 hour nap or nap plus relaxation (with perhaps graded sunbathing *a la* Becker) followed if possible by 1 hour of a hobby, in sanctuary.

9. Conversational exploration of simpler conflicts (often part of a total person history) with adjustment suggestions.

10. Systematic practice at living in the moment and viewing life with serene detachment. (The "big and little Mary device" helps.)

11. Systematic encouragement, with practice in self-esteem and self-acceptance.

12. Education of the patient in the recognition of his own tension signs including watching his own voice, hand, eye, and forehead, and application of remedies.

When the assistance of the psychiatrist or an adequate psychoanalyst can be secured, results obtainable in no other way are occasionally forthcoming. On the other hand, this method has been employed too infrequently and, frankly, with too little comprehension on the part of either psychiatrist or dermatologist of the interacting mechanisms in the causal background of the psychoneurodermatoses, the allergic-infective conditions, and so forth. The psychoanalytic successes have been sufficiently referred to in the foregoing discussion. Hypnosis has

also been sufficiently discussed. The use of suggestion by methods applicable in office practice for example, particularly suggestion during the early stages of anesthesia and the intravenous use of sedative drugs, is a new field as yet relatively unexplored. Eaton and O'Leary[22] describe the use of intravenous sodium amytal as an aid to psychotherapy in a case of dermatitis artefacta. "The patient, a fourteen-year-old girl, a victim of sex trauma, was given intravenously a solution of sodium amytal, containing 1 grain per cc. at the rate of 1 grain each minute. When 3 grains had been given, the patient became drowsy and the injection was discontinued. No excited stage was observed. After administering 1 to 6 grains of sodium amytal by the aforementioned technique, a period of exhilaration, excitement and talkativeness is usually produced. This is the effect desired and indicates that a sufficient amount of the drug has been given. If no excitatory stage is reached, enough is given to make the patient drowsy. Lorenz[44] recommended that the drug be administered until the corneal reflex is lost.

"When the patient gave evidence of inebriation from amytal, she was again told that the skin lesions were produced by herself during sleep. It was explained that her troubled sleep resulted from her subconscious distress over some experience she had undergone. It was suggested that she could remember the situation by letting her mind dwell on the events prior to her illness. Within a few minutes she recalled a psychically traumatic situation and discussed it freely. In this case the diagnostic value of the use of amytal is emphasized as the principal worth of the method." Campbell[18] employed sodium evipan intravenously as a preliminary to suggestion or analysis in doses of 2 to 8 cc. of 5 or 10% solution. The best time for analysis is after treatment. Campbell used this treatment in various conditions including 4 patients with neurodermatitis (group of skin conditions in which the precipitating factor is an anxiety state). He found that sodium evipan was of great value in producing a state of artificial hypnosis, and shortening psychoanalysis considerably.

It is never out of place to emphasize at the conclusion of any discussion of psychoneurogenous factors in disease that they appear far more often as components than they do as single causes. Inevitably the etiologic complexities will drag into the situation human viewpoints expressed by specialists in one field or another which need reconciliation that can only be obtained by a thorough-going coöperative study of the disease entities concerned. Here is the point at which the greatest prospect of advance in the psychoneurogenous field exists at the present time. When the dermatologist, through a coöperative arrangement, can share with the psychiatrist a general knowledge of the causative background of skin diseases, and can receive from the psychiatrist in a terminology that he can understand some degree of technical illumination as to the action of emotional factors, an entirely new and promising situation will develop.

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REFERENCES.

(1.) **Alkiewicz, J.**: Derm. Wchnschr., **98**, 519, 1934. (2.) **Allendy, R.**: Psychoanalyt. Rev., **19**, 152, 1932. (3.) **Allington, H. V.**: Arch. Derm. and Syph., **29**, 687, 1934. (4.) **Aubrun, E. A.**: "Pelada Experimental" de Max Joseph (prurito e hiperestesia por seccion nerviosa) Lopez, Buenos Aires, 1931. (5.) **Barinbaum, M.**: Zentralbl. f. Psychother., **5**, 106, 1932. (6.) **Bartemeier, L. H.**: Psychoanal. Quart., **7**, 216, 1938. (7.) **Becker, S. W.**: (*a*) Arch. Derm. and Syph., **12**, 235, 1925; (*b*) Ibid., **25**, 655, 1932; (*c*) **Becker, S. W.** and **Obermayer, M. E.**: Modern Dermatology and Syphilology, Philadelphia, J. B. Lippincott Company, 1940. (8.) **Beeson, B. B.**, and **Pickett, W. J.**: Arch. Derm. and Syph., **28**, 53, 1933. (9.) **Bettmann.**: Deutsch. Ztschr. f. Nervenheilk., **18**, 345, 1900. (10.) **Biberstein, H.**: Klin. Wchnschr., **4**, 638, 1925. (11.) **Bloch, B.**: Ibid., **6**, 2271, 2320, 1927. (12.) **Blocq, P.**: Gaz. hebd. de méd., May, 1891. (13.) **Brill, E.**: Arch. f. Dermat. u. Syph., **150**, 529, 1926. (14.) **Brown, F. W.**: Guy's Hosp. Rep., **88**, 356, 1938. (15.) **Brown, G. E.**: Am. J. Med. Sci., **183**, 463, 1932. (16.) **Brown, W. H.**: Brit. J. Dermat. and Syph., **41**, 299, 1929. (17.) **Bunnemann, O.**: Ztschr. f. d. Neurol. u. Psychiat., **88**, 589, 1924. (18.) **Campbell, A. M. G.**: Guy's Hosp. Rep., **88**, 185, 1938. (19.) **Cormia, F. E.**: (*a*) Arch. Derm. and Syph., **30**, 45, 1934; (*b*) —, and **Slight, D.**: Canad. Med. Assn. J., **33**, 527, 1935. (20.) **Diehl, F.**, and **Heinichen, W.**: Münch. med. Wchnschr., **78**, 1008, 1931. (21.) **Dunbar, H. F.**: Am. J. Psychiat., **95**, 1277, 1939. (22.) **Eaton, L. M.**, and **O'Leary, P. A.**: Proc. Staff Meet. Mayo Clin., **12**, 67, 1937; Arch. Derm. and Syph., **36**, 544, 1937. (23.) **Eller, J. J.**: Med. J. and Rec., **129**, 481, 554, 616, 675, 1929. (24.) **Eppinger, H.**, and **Hess, L.**: Ztschr. f. klin. Med., **68**, 205, 1909. (25.) **Genner, V.**: Etudes cliniques sur la pelade, Copenhagen, Levin and Munksgaard, 1929. (26.) **Gillespie, R. D.**: (*a*) Guy's Hosp. Rep., **88**, 172, 1938; (*b*) Brit. J. Derm. and Syph., **50**, 1, 1938. (27.) **Goeckermann, W. H.**: Med. Clin. North America, **14**, 645, 1930. (28.) **Goldsmith, W. N.**: Recent Advances in Dermatology, London, J. & A. Churchill, Ltd., 1931. (29.) **Goodman, H.**: Am. Med., **40**, 123, 1934. (30.) **Gossip, W. H.**: Brit. Med. J., 1, 69, 1937. (31.) **Harmer, I. M.**, and **Harris, K.**: Heart, **13**, 381, 1926. (32.) **Hartson, L.**: Brit. J. Derm. and Syph., **41**, 109, 1929.

(33.) **Haxthausen, H.**: (*a*) Acta dermat.-venereol., **13**, 408, 1932; (*b*) Brit. J. Derm. and Syph., **48**, 563, 1936. (34.) **Herrick, R.**: Arch. Derm. and Syph., **26**, 879, 1932. (35.) **Hunt, E.**: Lancet, 1, 592, 1936. (36.) **Jacobson, E.**: (*a*) Progressive Relaxation: A Physiological and Clinical Investigation of Muscular States and Their Significance in Psychology and Medical Practice, Chicago, University of Chicago Press, 1929; (*b*) You Must Relax: A Practical Method of Reducing the Strains of Modern Living, New York, McGraw Hill, 1934. (37.) **Jelliffe, S. E.**, and **Evans, E.**: New York Med. J., **104**, 1077, 1916. (38.) **Joseph, M.**: Monatsh. f. prakt. Dermat., **5**, 483, 1886. (39.) **Kartamischew, A. I.**: (*a*) Derm. Wchnschr., **96**, 788, 1933; (*b*) Ibid., **102**, 260, 1935; (*c*) Arch. f. Derm. and Syph., **174**, 36, 1936; (*d*) Derm. Wchnschr., **102**, 711, 1936 (see also : **Wisch, J. M.**: Derm. Wchnschr., **100**, 234, 1935). (40.) **Kelman, H.**, and **Field, H.**: J. Nerv. and Ment. Dis., **88**, 627, 1938. (41.) **Klaber, R.**, and **Wittkower, E.**: Brit. J. Derm. and Syph., **51**, 501, 1939. (42.) **Klauder, J. V.**: (*a*) J. Nerv. and Ment. Dis., **84**, 249, 1936; (*b*) Arch. Derm. and Syph., 37, 650, 1938. (43.) **Kreis, J.**: Gynecologie, **36**, 485, 1937. (44.) **Lorenz, W. F.**: Wisconsin Med. J., **31**, 245, 1932. (45.) **Loveman, A. B.**: Arch. Derm. and Syph., 28, 369, 1933. (46.) **MacCormac, H.**: Brit. Med. J., **2**, 1153, 1937. (47.) **MacKee, G. M.**: Arch. Derm. and Syph., **1**, 256, 1920. (48.) **Montgomery, D. W.**, and **Culver, G. D.**: Ibid., **26**, 474, 1932. (49.) **Netherton, E. W.**: J. Am. Med. Assn., 100, 722, 1933. (50.) **O'Donovon, W. J.**: Dermatological Neuroses, London, Kegan Paul, French, Trubner & Co., 1927. (51.) **Pearson, G. H. J.**: Psychosomatic Med., 2, 22, 1940. (52.) **Prosser-Thomas**: Brit. J. Med., **1**, 805, 1937. (53.) **Ramel, E.**: Schweiz. Arch. f. Neurol. u. Psych., **43**, 130, 1939. (54.) **Rasch**: Hospitalstidende, p. 797, 1898. (55.) **Ravaut** and co-workers: (*a*) Precis de Dermatologique, Paris, Masson et Cie, 4th ed., 1928; (*b*) Presse méd., **35**, 1443, 1928; Bull. Soc. franc. de dermat. et syph., **36**, 170, 1928; Bull. Acad. de méd., Paris, **101**, 680, 1929; Bull. Soc. franc. de dermat. et syph., **37**, 561, 1930; (*c*) Rev. méd. de la Suise Romande, **49**, 887, 1925. (56.) **Rogerson, C. H.**: (*a*) Quart. J. Med., **6**, 367, 1937; (*b*) Practitioner, **142**, 17, 1939; (*c*) Bibliography of previous review. (57.) **Roxburgh, A. C.**: Brit. J. Derm. and Syph., **41**, 351, 1929. (58.) **Sack, W. T.**: Psyche und Haut und Geschlechtskrankheiten, Berlin, Julius Springer, IV/**2**, 1302, 1933. (59.) **Saegesser, M.**: Schweiz. med. Wchnschr., **68**, 1409, 1938. (60.) **Sellei, J.**: Brit. J. Derm., **46**, 523, 1934. (61.) **Stokes, J. H.** et al.: (*a*) Arch. Derm. and Syph., **22**, 803, 1930; (*b*)

Med. Clin. North America, **15**, 279, 1931; (*c*) J. Am. Med. Assn., **105**, 1007, 1935; (*d*) Internat. Clin., **1** (Ser. 3), 147, 1940; Arch. Derm. and Syph., in press; (*e*) Arch. Derm. and Syph., **26**, 478, 1932; Ibid., **29**, 874, 1934; (*f*) J. Am. Med. Assn., **93**, 438, 1929; (*g*) Arch. Derm. and Syph., **31**, 470, 1935. (**62.**) **Sulzberger, M. B.**, and **Wolf, J.**: Med. Rec., **140**, 552, 1934. (**63.**) **Szondi, L.**: Arch. f. Derm. u. Syph., **154**, 53, 1927. (**64.**) **Vignolo-Lutati, C.**: Policlinico, **25**, 680, 1918. (**65.**) **Vorhees**: J. Am. Med. Assn., **48**, 1837, 1907. (**66.**) **Williams, D. H.**: J. Invest. Derm., **1**, 119, 1938. (**67.**) **Wright, C. S.**: Arch. Derm. and Syph., **19**, 365, 1929.

Correction:—In Dr. Altshuler's article on "Maintenance of Nitrogen Equilibrium of Amino Acids Administered Parenterally" in the August, 1940, number, the word "nitrogen" should be omitted on page 240, line 27.

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